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(21) International Application Number: PCT/US90/03367 (22) International Filing Date: 12 June 1990 (12.06.90) (30) Priority data: 365,349 13 June 1989 (13.06.89) US (60) Parent Application or Grant (63) Related by Continuation US 365,349 (CIP) Filed on 13 June 1989 (13.06.89) (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only) : BADGER, Alison, Mary [US/US]; 56 Parkridge Drive, Bryn Mawr, PA 19010 (US). BENDER, Paul, Elliot [US/US]; 504 Lilac Lane, Cherry Hill, NJ 08003 (US). ESSER, Klaus, Max [US/US]; 200 Hickory Drive, Downingtown, PA 19335 (US). GRISWOLD, Don, Edgar [US/US]; 205 Lower Valley Road, North Wales, PA 19454 (US). NABIL, Hanna [US/US]; 539 Sierra #108, Solana Beach, CA 92075 (US). LEE, John, C. [US/US]; 245 Gulph Hills Road, Radnor, PA 19087 (US). VOTTA, Bartholomew, Jude [US/US]; 1465 North Valley Road, Pottstown, PA 19464 (US). SIMON, Philip, Leonard [US/US]; 18 Leigh Court, Randolph, NJ 07869 (US). (74) Agents: DINNER, Dara, L. et al.; Corporate Patents - U.S., N160, SmithKline Beecham Corporation, P.O. Box 7929, Philadelphia, PA 19101 (US). (81) Designated States: AU, CA, JP, KR, US. Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: INHIBITION OF INTERLEUKIN-1 AND TUMOR NECROSIS FACTOR PRODUCTION BY MONOCYTES AND/OR MACROPHAGES (57) Abstract <p>A method of inhibiting the production of interleukin-1 by monocytes and/or macrophages in a human in need thereof which comprises administering to such a human an effective, interleukin-1 production inhibiting amount of a diaryl-substituted imidazole fused to a second heterocyclic ring containing a nitrogen bridgehead atom wherein said second ring may also contain sulfur, oxygen or an additional nitrogen atom, and may contain additional unsaturation. This invention relates to a method of inhibiting the production of Tumor Necrosis Factor (TNF) by monocytes or macrophages in a human in need thereof which comprises administering to such mammal an effective, TNF production inhibiting amount of a compound of formula (I) as described herein. The compounds of formula (II) are generally described as diaryl-substituted imidazole fused to a second heterocyclic ring containing a nitrogen bridgehead wherein said ring may also contain sulfur, oxygen, or an additional nitrogen atom, and may contain additional unsaturation.</p>		

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TITLEINHIBITION OF INTERLEUKIN-1 AND TUMOR NECROSIS FACTOR
PRODUCTION BY
MONOCYTES AND/OR MACROPHAGES

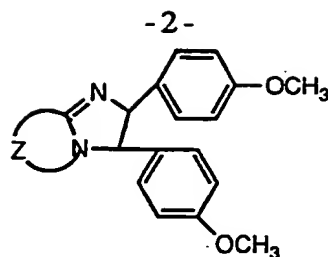
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BACKGROUND OF THE INVENTION

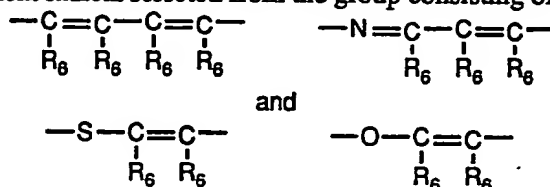
20 This invention relates to a method of inhibiting the production of interleukin-1 by monocytes and/or macrophages in a human in need thereof which comprises administering to such human an effective, interleukin-1 production inhibiting amount of a diaryl-substituted imidazole fused to a second heterocyclic ring containing a nitrogen bridgehead atom wherein said second ring may also contain sulfur, oxygen or an additional nitrogen atom, and may contain additional unsaturation.

25 This invention relates to a method of inhibiting the production of Tumor Necrosis Factor (TNF) by monocytes or macrophages in a mammal in need thereof which comprises administering to such mammal an effective, TNF production inhibiting amount of a compound of Formula (II) as described herein. The compounds of Formula (II) are generally described as diaryl-substituted imidazole fused to a second heterocyclic ring containing a nitrogen bridgehead
30 wherein said ring may also contain sulfur, oxygen, or an additional nitrogen atom, and may contain additional unsaturation.

Lednicer, U.S. Patent Number 3,455,924, issued July 15, 1969, describes compounds of the formula:



wherein Z is a bivalent radical selected from the group consisting of:



in which up to two of the parameters R_1 , R_2 , R_3 and R_4 are selected from the group consisting of hydrogen, lower alkyl and lower alkoxy having 1 to 4 carbon atoms, inclusive, hydroxy and nitro and the remaining parameters are hydrogen.

Adams *et al.*, U.S. Patent Application Serial Number 07/255,816, filed October 11, 1988, generically discloses pyrrolyl substituted pyrrolo-[2,1-a]-imidazoles and pyridines as useful for inhibiting the 5-lipoxygenase pathway of arachadonic acid metabolism in an animal in need thereof. Specifically disclosed are the following compounds:

2-(4-methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole;

2-(4-methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;

2-(4-ethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;

2-(4-ethylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;

2-(4-methylthiophenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;

2-(4-methylsulfinylphenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;

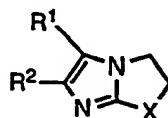
6-(4-methylthiophenyl)-5-(4-pyridyl)-2,3-dihydro-imidazo[2,1-b]thiazole;

5-(4-methylthiophenyl)-6-(4-pyridyl)-2,3-dihydro-imidazo[2,1-b]thiazole; and

3-(4-methylthiophenyl)-2-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole.

Bender *et al.*, U.S. Patent Number 4,794,114, issued December 27, 1988, disclose a method of inhibiting the production of IL-1 by monocytes and/or

macrophages in a human in need thereof which comprises administering to such human an effective, interleukin-1 production inhibiting amount of a compound of the formula:



5 wherein:

One of R¹ and R² must be 4-pyridyl and the other is selected from monosubstituted phenyl wherein said substituent is selected from halo or C₁₋₄ alkoxy; X is CH₂, CH₂CH₂ or S(O)_n; and n is 0, 1 or 2;

10 or a pharmaceutically acceptable salt thereof.

Dinareello *et al.*, *Int. J. Immunopharmacology*, 6(1), 43-50 (1984), suggest that a product of arachidonate lipoxygenase is important in the sequence of events underlying cell activation for the production of human interleukin-1.

15 Griswold *et al.*, *Inflammation*, 11(2), 189-199 (1987), discuss the inhibitory effects of 5-(4-pyridyl)-6(4-fluorophenyl)-2,3-dihydroimidazo-(2,1-b)thiazole and other dual inhibitors of arachidonic acid metabolism (i.e., inhibitors of 5-lipoxygenase and cyclooxygenase mediated arachidonate metabolism) on the edematous and cellular component of arachidonic acid-induced inflammation.

20 Lee *et al.*, *Int. J. Immunopharmac.*, 10(7), 835-843 (1988), discuss that [5-(4-pyridyl)-6(4-fluorophenyl)-2,3-dihydroimidazo(2,1-b)thiazole], which inhibits both 5-lipoxygenase and cyclooxygenase-mediated arachidonate metabolism, was shown to be a potent inhibitor of IL-1 production by bacterial lipopolysaccharide (LPS)-stimulated human monocytes, and that other cyclooxygenase and/or 5-lipoxygenase inhibitors of arachidonic acid metabolism tested, with the exception of 25 nordihydroguaiaretic acid, were inactive in inhibiting monocyte IL-1 production suggesting that the inhibition of IL-1 production by 5-(4-pyridyl)-6(4-fluorophenyl)-2,3-dihydroimidazo-(2,1-b)thiazole may be dissociated from its inhibition of fatty acid oxygenases.

30 There remains a need for compounds which are useful in inhibiting the production of interleukin-1 (IL-1) by monocytes and/or macrophages in a human in need of such inhibition.

35 Studies have indicated that TNF is a glycoprotein and that its activity is associated with high molecular weight components. Mouse and rabbit TNF have been isolated, as has human TNF which sequence is taught in US Patent 4,879,226, issued November 7, 1989. TNF is synthesized as a prohormone and subsequently cleaved at several sites to yield the mature hormone. While the active polypeptide itself has been evaluated for treatment of tumors due to its earlier reported antineoplastic activity, this administration has not

been without may severe toxicities. Overproduction of TNF has further been implicated in the pathogenesis of endotoxin/septic shock, See e.g., Carswell et al., Proc. Natl. Acad. Sci. USA, 72, 3666-3670 (1975). Endotoxin is the lipopolysaccharide component of the cell wall of gram-negative bacteria, and is a macrophage activator which induces the synthesis and secretion of cytokines and other biologically active molecules such as TNF. In sepsis, TNF production leads to hypotension, vascular endothelial permeability, and organ damage, i.e., some of the results of endotoxic shock. Adult Respiratory Distress Syndrome (ARDS) is frequently associated with sepsis and multiple organ failure which has led to the suggested role of TNF in the pathogenesis of ARDS. TNF is also the agent responsible for the weight loss (cachexia) found in chronic catabolic disease states, such as long term parasitic and viral infections and malignancies. This weight loss is a handicap to recovery and may even be fatal.

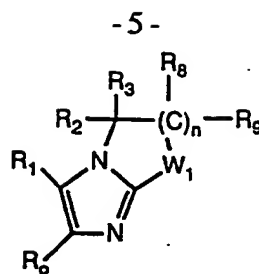
TNF also appears to play a role as an early product in the inflammatory response. See e.g., Old, Nature, 330, 602-03 (1987). It further appears that among the cytokines, while TNF production precedes and augments the function of IL-1 and other cytokines there is no clear data on how the relationship among these molecules contributes to inflammation-related disease states. TNF activates macrophages and enhances their cytotoxic potential in vitro. TNF has been shown to be chemotactic for monocytes, suggesting that the production of TNF at sites of injury may function to recruit additional macrophages and activate those macrophages already present.

Among the various mammalian conditions for which TNF is implicated in mediating or exacerbating rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acute immune deficiency syndrome (AIDS), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or other inflammatory skin conditions such as pyresis.

The ability to control the adverse effects of TNF is furthered by the use of the compounds of this invention for humans who are in need of such use. There remains a need for compounds which are useful in inhibiting the production of tumor necrosis factor (TNF) by monocytes and/or macrophages in a human in need of such inhibition.

SUMMARY OF THE INVENTION

This invention relates to a method of inhibiting the production of interleukin-1 (IL-1) by monocytes and/or macrophages in a human in need thereof which comprises administering to such human an effective, IL-1 production inhibiting amount of a compound of the formula



FORMULA (I)

wherein:

5 W_1 is $-(CR_4R_5)-(CR_6R_7)-$, $-CR_5=CR_7-$, $-N=CR_7-$, $-S(O)_m-$ or $-O-$;
one of R_1 and R_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that
when R_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the
pyridine ring, and the other of R_1 and R_0 is

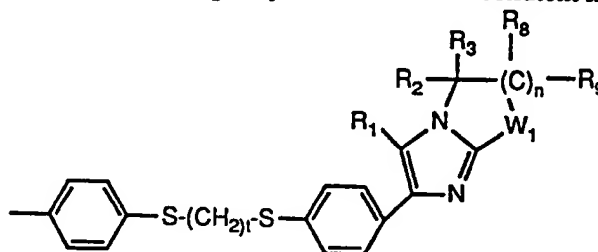
(a) phenyl or monosubstituted phenyl wherein said
substituent is C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio,
10 C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-
sulfinyl, 1-acyloxy-1-alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl or Z
wherein Z is $-S-S-Z_1$ and Z_1 is phenyl or C_{1-9} alkyl; or

(b) disubstituted phenyl wherein said substituents are,
independently, C_{1-3} alkylthio, C_{1-2} alkoxy, halo or C_{1-4} alkyl; or

15 (c) disubstituted phenyl wherein one of said substituents is C_{1-3}
alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-
alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio and
the other is C_{1-2} alkoxy, halo, or C_{1-4} alkyl; or

20 (d) disubstituted phenyl wherein the substituents are the same
and are C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-
sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-
1-alkylthio or wherein the substituents together form a methylene dioxy
group; or

(e) monosubstituted phenyl wherein said substituent is



25 t is 0 or 1; W_1 , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are as defined
above;

provided that:

(1.) when W_1 is $-(CR_4R_5)-(CR_6R_7)-$ then

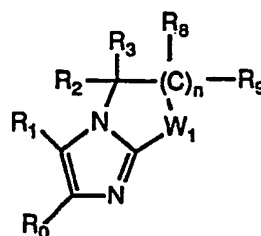
- n is 0 or 1;
and R₂, R₃, R₄, R₅, R₆, R₇, R₈, and R₉ are, independently, -H or C₁₋₂ alkyl; and when R₁ or R₀ is 4-pyridyl, the other of R₁ and R₀ is other than mono-C₁₋₂ alkoxy-substituted phenyl or mono-halo-substituted phenyl; or
when n is 0, R₄ and R₅ together are oxo; R₄ and R₅ are both fluoro, or one of R₄ and R₅ is H and the other is OH;
- (2.) when W₁ is -CR₅=CR₇- or -N=CR₇- then
n is 1;
R₃, R₅, R₇ and R₉ are, independently, -H or C₁₋₂ alkyl; and
R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring;
- (3.) when W₁ is S(O)_m then
m is 0, 1 or 2;
n is 1 or 2; and
R₃ and R₉ are, independently, -H or C₁₋₂ alkyl;
R₂ and R₈ are, independently, -H or C₁₋₂ alkyl or R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring;
- further provided that:
(a) when R₂ and R₈ are, independently, -H or C₁₋₂ alkyl and R₁ or R₀ is 4-pyridyl, then the other of R₁ and R₀ is other than mono-C₁₋₂ alkoxy-substituted phenyl or mono-halo-substituted phenyl; and
(b) when R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring, then m is 0 and n is 1; and
- (4) when W₁ is -O- then
n is 1;
R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; and
R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring

or a pharmaceutically acceptable salt thereof.

- This invention further relates to the intermediate compounds of Formulas C, D, E, F, If, and G.

This invention also relates to a method of inhibiting the production of tumor necrosis factor (TNF) by monocytes and/or macrophages in a human in need

thereof which comprises administering to such human an effective, TNF production inhibiting amount of a compound of the Formula (II).



FORMULA (II)

wherein:

W₁ is -(CR₄R₅)-(CR₆R₇)-, -CR₅=CR₇-, -N=CR₇-, -S(O)_m- or -O-;
one of R₁ and R₀ is 4-pyridyl or C₁₋₄ alkyl-4-pyridyl,
provided that when R₁ is C₁₋₄ alkyl-4-pyridyl the alkyl substituent is
located at the 2-position of the pyridine ring, and the other of R₁ and
R₀ is

(a) phenyl or monosubstituted phenyl wherein said
substituent is C₁₋₃ alkylthio, C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-thio,
C₂₋₅ 1-alkenyl-1-sulfinyl, C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-
sulfinyl, 1-acyloxy-1-alkylthio, C₁₋₂ alkoxy, halo, C₁₋₄ alkyl or Z
wherein Z is -S-S- Z₁ and Z₁ is phenyl or C₁₋₉ alkyl; or

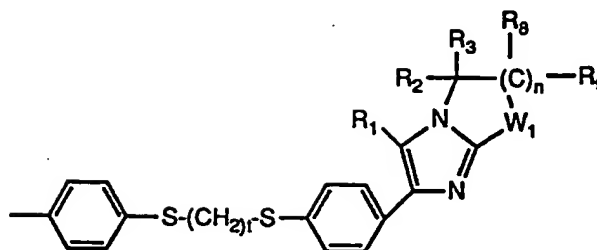
(b) disubstituted phenyl wherein said substituents are,
independently, C₁₋₃ alkylthio, C₁₋₂ alkoxy, halo or C₁₋₄ alkyl; or

(c) disubstituted phenyl wherein one of said substituents is
C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-thio, C₂₋₅ 1-alkenyl-1-sulfinyl,
C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-sulfinyl or 1-acyloxy-1-
alkylthio and the other is C₁₋₂ alkoxy, halo, or C₁₋₄ alkyl;

(d) disubstituted phenyl wherein the substituents are the same
and are C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-thio, C₂₋₅ 1-alkenyl-1-
sulfinyl, C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-sulfinyl or 1-
acyloxy-1-alkylthio or wherein the substituents together form a
methylene dioxy group; or

(e) monosubstituted phenyl wherein the substituent is

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t is 0 or 1; W₁, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and R₉ are as defined above;

provided that:

- 5 (1.) when W₁ is -(CR₄R₅)-(CR₆R₇)- then
 n is 0;
 a) and R₄ and R₅ may together form an oxo; R₄ and R₅ are both fluoro; or one of R₄ and R₅ is H and the other OH; or
- 10 (2.) when W₁ is -CR₅=CR₇- or -N=CR₇- then
 n is 1;
 R₃, R₅, R₇ and R₉ are, independently, -H or C₁₋₂ alkyl; and
 R₂ and R₈ together represent a double bond in the B ring such that the
 15 B ring is an aromatic pyridine or pyrimidine ring;
- (3.) when W₁ is S(O)_m then
 m is 0, 1 or 2;
 n is 1 or 2; and
 R₃ and R₉ are, independently, -H or C₁₋₂ alkyl;
 20 R₂ and R₈ are, independently, -H or C₁₋₂ alkyl or R₂ and R₈
 together represent a double bond in the B ring such that the B ring is
 an aromatic thiazole ring;
 further provided that:
 (a) when R₂ and R₈ are, independently, -H or C₁₋₂ alkyl and
 25 R₁ or R₉ is 4-pyridyl, then the other of R₁ and R₉ mono-
 fluoro-substituted phenyl; and
 (b) when R₂ and R₈ together represent a double bond in the B
 ring such that the B ring is an aromatic thiazole ring, then m is
 0 and n is 1; and
- 30
- (4) when W₁ is -O- then

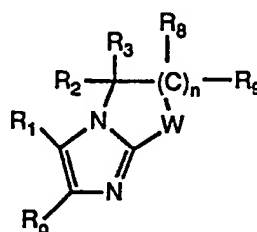
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n is 1;

R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; andR₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring;

5 or a pharmaceutically acceptable salt thereof.

This invention also relates to a compound of Formula (IA) and the process of making a compound of Formula (IA):



FORMULA (IA)

wherein:

W is -CR₅=CR₇-, -N=CR₇-, -S(O)_m- or -O-;

one of R₁ and R₀ is 4-pyridyl or C₁₋₄ alkyl-4-pyridyl, provided that when R₁ is C₁₋₄ alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R₁ and R₀ is

15 (a) monosubstituted phenyl wherein said substituent is C₁₋₃ alkylthio, C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-thio, C₂₋₅ 1-alkenyl-1-sulfinyl, C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-sulfinyl, 1-acyloxy-1-alkylthio, C₁₋₂ alkoxy, halo, C₁₋₄ alkyl, or Z wherein Z is -S-S-Z₁ and Z₁ is phenyl or C₁₋₉ alkyl; or

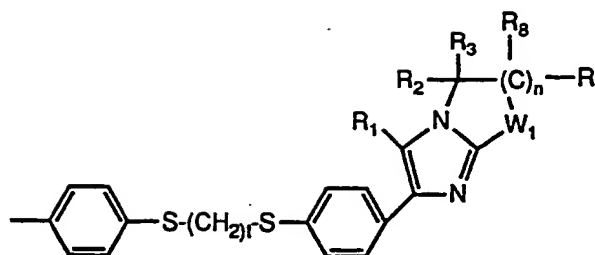
20 (b) disubstituted phenyl wherein said substituents are, independently, C₁₋₃ alkylthio, C₁₋₂ alkoxy, halo or C₁₋₄ alkyl; or

25 (c) disubstituted phenyl wherein one of said substituents is C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-thio, C₂₋₅ 1-alkenyl-1-sulfinyl, C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio and the other is C₁₋₂ alkoxy, halo, or C₁₋₄ alkyl;

30 (d) disubstituted phenyl wherein the substituents are the same and are C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-thio, C₂₋₅ 1-alkenyl-1-sulfinyl, C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group; or

(e) monosubstituted phenyl wherein said substituent is

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t is 0 or 1; W_1 , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are as in Formula (I);

provided that:

- 5 (1.) when W is $-CR_5=CR_7-$ or $-N=CR_7-$ then
 - n is 1;
 - R_3 , R_5 , R_7 and R_9 are, independently, $-H$ or C_{1-2} alkyl;
 - R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and
- 10 (2.) when W is $S(O)_m$;
 - m is 0, 1 or 2;
 - n is 1 or 2;
 - R_3 and R_9 are, independently, $-H$ or C_{1-2} alkyl; and
 - R_2 and R_8 are, independently, $-H$ or C_{1-2} alkyl; then
 - 15 one of R_1 or R_0 is 4-pyridyl, and the other of R_1 and R_0 is:
 - (a) monosubstituted phenyl wherein said substituent is selected from C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, 1-acyloxy-1-alkylthio; or
 - 20 (b) disubstituted phenyl wherein said substituents are independently selected from C_{1-3} alkylthio or halo; or
 - (c) disubstituted phenyl wherein one of said substituents must be C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio and the other is selected from
 - 25 C_{1-2} alkoxy, halo or C_{1-4} alkyl; and
- (3.) when W is $S(O)_m$;
 - m is 0;
 - n is 1; and
 - 30 R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; then
 - R_3 and R_9 are, independently, $-H$ or C_{1-2} alkyl; and
- (4.) when W is $-O-$ then
 - n is 1;

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R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; and

R₂ and R₈ together represent a double bond in the B ring such that the

B ring is an aromatic oxazole ring; or

or a pharmaceutically acceptable salt thereof.

5 This invention also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (IA) and a pharmaceutically acceptable carrier or diluent.

DETAILED DESCRIPTION OF THE INVENTION

10 It will be apparent to one of skill in the art that all the compounds of Formula (IA) are embraced within the scope of the compounds of Formula (I). The compounds of Formula (I) are also embraced within the scope of the compounds of Formula (II). The compounds of Formula (I) differ from the compounds of Formula (II) wherein W₁ is -(CR₄R₅)-(CR₆R₇)- and when W₁ is S(O)_m. The compounds of Formula (II) do not have the following proviso language:

15 when W₁ is -(CR₄R₅)-(CR₆R₇)- then;

n is 0 or 1;

and R₂, R₃, R₄, R₅, R₆, R₇, R₈, and R₉ are, independently, -H or C₁₋₂ alkyl; and when R₁ or R₀ is 4-pyridyl, the other of R₁ and R₀ is other than mono-C₁₋₂ alkoxy-substituted phenyl or mono-halo-

20 substituted phenyl; or

when W₁ is S(O)_m then

m is 0, 1 or 2;

n is 1 or 2; and

R₃ and R₉ are, independently, -H or C₁₋₂ alkyl;

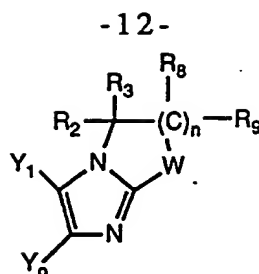
25 R₂ and R₈ are, independently, -H or C₁₋₂ alkyl

further provided that:

(a) when R₂ and R₈ are, independently, -H or C₁₋₂ alkyl and R₁ or R₀ is 4-pyridyl, then the other of R₁ and R₀ is other than mono-C₁₋₂ alkoxy-substituted phenyl or mono-halo-substituted phenyl.

30 In addition to the methods of the present invention, and the compounds of Formula (IA) this invention also relates to the intermediate compounds shown below.

This invention relates to a compound of the formula :



FORMULA (D)

, or a pharmaceutically acceptable salt thereof,

5 wherein:

W is -CR₅=CR₇-, -N=CR₇-, -S- or -O-;

Y₁ is 4-(1,4-dihydro)pyridyl substituted with N-(C₁₋₈ alkanoyl), N-(C₁₋₈ alkoxy carbonyl), N-benzoyl, N-phenoxy carbonyl, N-phenylacetyl, or N-benzyloxycarbonyl;

10 Y₀ is (a) monosubstituted phenyl wherein said substituent is C₁₋₃ alkylthio, C₁₋₂ alkoxy, halo, -H, or C₁₋₄ alkyl; or (b) disubstituted phenyl wherein said substituents are, independently, C₁₋₃ alkylthio, C₁₋₂ alkoxy, halo, C₁₋₄ alkyl, or the disubstituents together form a methylene dioxy group;

15 provided that:

(1.) when W is -CR₅=CR₇- or -N=CR₇- then

n is 1;

R₃, R₅, R₇ and R₉ are, independently, -H or C₁₋₂ alkyl;

20 R₂ and R₈ together represent a double bond across the two adjacent carbon atoms in the B ring so as to form an aromatic pyridine or pyrimidine ring; and

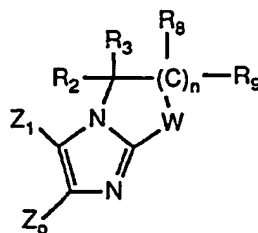
(2.) when W is -S- or -O- then

n is 1;

R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; and

25 R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole or oxazole ring.

This invention also relates to a compound of the formula:



FORMULA (E)

, or a pharmaceutically acceptable salt thereof,
wherein:

5 W is $-\text{CR}_5=\text{CR}_7-$, $-\text{N}=\text{CR}_7-$, $-\text{S}-$ or $-\text{O}-$;
one of Z_1 and Z_0 is 4-(1,2-dihydro-2-alkyl)pyridyl substituted with N-(C1-8 alkanoyl), N-(C1-8 alkoxy carbonyl), N-benzoyl, N-phenoxy carbonyl, N-phenylacetyl, or N-benzyloxy carbonyl; and the other of Z_1 and Z_0 is

10 (a) monosubstituted phenyl wherein said substituent is selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, $-\text{H}$, or C_{1-4} alkyl; or

(b) disubstituted phenyl wherein said substituents are independently selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl, or the disubstituents together form a methylene dioxy group;

provided that:

15 (1.) when W is $-\text{CR}_5=\text{CR}_7-$ or $-\text{N}=\text{CR}_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are, independently, $-\text{H}$ or C_{1-2} alkyl;

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

20 (2.) when W is $-\text{S}-$ or $-\text{O}-$ then

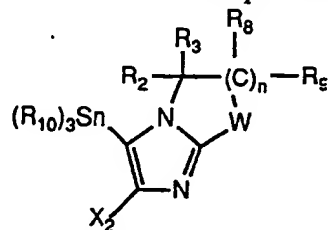
n is 1;

R_3 and R_9 are, independently, $-\text{H}$ or C_{1-2} alkyl; and

R_2 and R_8 are, independently, $-\text{H}$ or C_{1-2} alkyl or together represent a double bond in the B ring such that the B ring is an aromatic thiazole or oxazole ring.

25

This invention also relates to a compound of the formula:



FORMULA (F)

30 wherein:

W is $-\text{CR}_5=\text{CR}_7-$, $-\text{N}=\text{CR}_7-$, $-\text{S}-$ or $-\text{O}-$;

R_{10} is C_{1-4} alkyl; and

X_2 is 4-pyridyl or mono- C_{1-4} alkyl-substituted pyridyl;

provided that:

- 14 -

(1.) when W is $-\text{CR}_5=\text{CR}_7-$ or $-\text{N}=\text{CR}_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are, independently, -H or C_{1-2} alkyl;

R_2 and R_8 together represent a double bond in the B ring such that the

5

B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is -S- then

n is 1 or 2;

R_3 and R_9 are, independently, -H or C_{1-2} alkyl;

further provided that:

10

(a) when W is -S- and n is 1 then R_2 and R_8 are, independently, -H or C_{1-2} alkyl or together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; and

(b) when W is -S- and n is 2 then R_2 and R_8 are, independently, -H or C_{1-2} alkyl; and

15 (3.) when W is -O- then

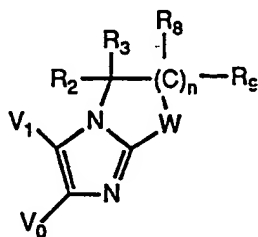
n is 1;

R_3 and R_9 are, independently, -H or C_{1-2} alkyl; and

R_2 and R_8 represent double bonds in the B ring such that the B ring is an aromatic oxazole ring.

20

This invention also relates to a compound of the formula:



FORMULA (G)

25 , or a pharmaceutically acceptable salt thereof,

wherein:

W is $-\text{CR}_5=\text{CR}_7-$, $-\text{N}=\text{CR}_7-$, -S- or -O-;

one of V_1 or V_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that

30 when V_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of V_1 and V_0 is selected from:

(a) monosubstituted phenyl wherein said substituent is mercapto;

or

(b) disubstituted phenyl wherein one of said

- 15 -

substituents must be mercapto and the other is selected from mercapto, C₁₋₂ alkoxy, halo, or C₁₋₄ alkyl;

provided that:

(1.) when W is -CR₅=CR₇- or -N=CR₇- then

5

n is 1;

R₃, R₅, R₇ and R₉ are, independently, -H or C₁₋₂ alkyl; and

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is -S- then

10

n is 1 or 2;

R₃ and R₉ are, independently, -H or C₁₋₂ alkyl;

further provided that:

15

(a) when W is -S- and n is 1 then R₂ and R₈ are, independently, -H or C₁₋₂ alkyl or together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; and

(b) when W is -S- and n is 2 then R₂ and R₈ are, independently, -H or C₁₋₂ alkyl; and

(3.) when W is -O- then

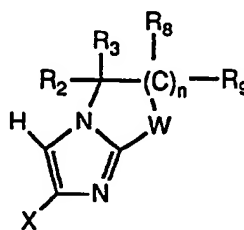
20

n is 1;

R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; and

R₂ and R₈ represent double bonds in the B ring such that the B ring is an aromatic oxazole ring.

This invention also relates to a compound of the formula:



25

FORMULA (C)

, or a pharmaceutically acceptable salt thereof,

30 wherein:

W is -CR₅=CR₇-, -N=CR₇-, -S- or -O-;

X is

a) 4-pyridyl or mono-C₁₋₄ alkyl-substituted pyridyl;

- 16 -

b) b) phenyl or monosubstituted phenyl wherein the substituent is selected from hydrogen, halo, C₁₋₄ alkyl, C₁₋₃ alkylthio, or C₁₋₂ alkoxy; or

5 c) disubstituted phenyl wherein the substituents are selected from halo, C₁₋₃ alkylthio, C₁₋₃ alkyl, C₁₋₂ alkoxy, or the disubstituents together form a methylene dioxy group;

provided that:

(1.) when W is -CR₅=CR₇- or -N=CR₇- then

n is 1;

10 R₃, R₅, R₇ and R₉ are, independently, -H or C₁₋₂ alkyl;

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is -S- then

n is 1 or 2;

15 R₃ and R₉ are, independently, -H or C₁₋₂ alkyl;

further provided that:

(a) when W is -S- and n is 1 then

20 R₂ and R₈ are, independently, -H or C₁₋₂ alkyl or together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; and

(b) when W is -S- and n is 2 then

R₂ and R₈ are, independently, -H or C₁₋₂ alkyl; and

(3.) when W is -O- then

n is 1;

25 R₃ and R₉ are, independently, -H or C₁₋₂ alkyl;

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring.

30 By the term "halo" as used herein is meant all halogens, i.e., chloro, fluoro, bromo and iodo.

By the term "inhibiting the production of IL-1" is meant the down regulation of excessive in vivo IL-1 levels in a human to normal levels.

By the term "production of IL-1 by monocytes and/or macrophages" is meant the in vivo release of IL-1 by such cells.

35 By the term "inhibiting the production of TNF" is meant the down regulation of excessive in vivo TNF levels in a human to normal levels.

By the term "production of TNF by monocytes and/or macrophages" is meant the in vivo release of TNF by such cells.

The discovery of a compound which specifically inhibits TNF production will not only contribute to the understanding of how this molecule is synthesized, processed and secreted, but will also provide a therapeutic approach for diseases in which excessive or unregulated TNF production is implicated. As TNF- β (also known as lymphotoxin) has close structural homology with TNF- α (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF- α and TNF- β are both inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

By the term "sulfinyl" as used herein is meant the oxide of the corresponding sulfide. By the term "thio" as used herein is meant the sulfide. For further clarification, the following table outlines the structural attachment of the atoms of the R_1 and R_0 substituents of the compounds of Formula (I) and Formula (II):

R_1 or R_0	Structural Attachment
C_{1-3} alkylsulfinyl	[AS(O)-]
C_{2-5} 1-alkenyl-1-thio	[AA ¹ C=CHS-]
C_{2-5} 1-alkenyl-1-sulfinyl	[AA ¹ C=CHS(O)-]
C_{3-5} 2-alkenyl-1-thio	[ACH=CA ¹ CH ₂ S-]
C_{3-5} 2-alkenyl-1-sulfinyl	[ACH=CA ¹ CH ₂ S(O)-]
1-acyloxy-1-alkylthio	[AC(O)OCH(A ¹)S-]

NOTE: A and A¹ are hydrogen or alkyl;

The preparation of all compounds of Formula (I) and (II) and pharmaceutically acceptable salts thereof wherein W_1 is $-(CR_4R_5)-(CR_6R_7)-$; n is 0 or 1; $R_2, R_3, R_4, R_5, R_6, R_7, R_8$ and R_9 are H or one or more of $R_2, R_3, R_4, R_5, R_6, R_7, R_8$ and R_9 are independently selected from H or C_{1-2} alkyl; and one of R_0 or R_1 is 4-pyridyl or mono- C_{1-4} alkyl-substituted-4-pyridyl, is disclosed in Bender *et al.*,

U.S. Patent Application Serial Number 07/255,816, filed October 11, 1988, the disclosure of which is hereby incorporated by reference.

The preparation of all compounds of Formula (I) and (II) and pharmaceutically acceptable salts thereof wherein W_1 is $S(O)_m$; m is 0, 1 or 2; n is 1 or 2; $R_2, R_3, R_4, R_5, R_6, R_7, R_8$ and R_9 are H or one or more of $R_2, R_3, R_4, R_5, R_6, R_7, R_8$ and R_9 are independently selected from H or C_{1-2} alkyl; and R_1 or R_0 is 4-pyridyl, other than those compounds wherein R_1 or R_0 is monosubstituted phenyl wherein said substituent is selected from C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{2-5} 2-alkenyl-1-thio or C_{2-5} 2-alkenyl-1-sulfinyl, 1-acyloxy-1-alkylthio or

disubstituted phenyl wherein said substituents are selected from one of the following combinations: di(C₁₋₃ alkylthio), dihalo, C₁₋₃ alkylthio and C₁₋₂ alkoxy, C₁₋₃ alkylthio and halo, C₁₋₃ alkylthio and C₁₋₄ alkyl, or C₁₋₂ alkoxy and halo, or disubstituted phenyl wherein the substituents are the same and are selected from; C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-thio, C₂₋₅ 1-alkenyl-1-sulfinyl, C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio, or disubstituted phenyl wherein one of said substituents must be C₁₋₃ alkylthio, C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-thio, C₂₋₅ 1-alkenyl-1-sulfinyl, C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio and the other is selected from C₁₋₂ alkoxy, halo, or C₁₋₄ alkyl is disclosed in Bender *et al.*, U.S. Patent Number 4,175,127, issued November 20, 1979, Bender *et al.*, U.S. Patent Application Serial Number 07/106,199 filed on July 10, 1987 or Bender *et al.*, U.S. Patent Number 4,803,279, issued February 9, 1989, the entire disclosures of all of which are hereby incorporated by reference.

The preparation of the compounds of Formula (II) and pharmaceutically acceptable salts thereof wherein W₁ is -(CR₄R₅)-(CR₆R₇)-; n is 0, R₄ and R₅ together are oxo; or when one of R₄ and R₅ is H the other of R₄ and R₅ is OH; or when R₄ and R₅ are both fluoro substituents are disclosed in Gallagher *et al.*, Tetrahedron Letters, Vol. 30, No. 48, pp.6599-6602 (1989) the entire disclosure of which is hereby incorporated by reference.

The preparation of all the remaining compounds of Formula (I) not already described above, including all the compounds of Formula (IA), can be carried out by one of skill in the art according to the procedures outlined in the Examples, *infra*.

All of the compounds of Formula (I) and (II) are useful in the methods of the subject invention, i.e. methods of inhibiting the production of IL-1 or TNF by macrophages and/or monocytes in a human in need thereof.

All the compounds of Formula (C), Formula (D), Formula (E), Formula (F) and Formula (G) are useful as intermediates in the preparation of the compounds of Formula (IA). The preparation of all the compounds of Formula (C), Formula (D), Formula (E), Formula (F) and Formula (G) can be carried out by one of skill in the art according to the procedures outlined in the Examples, *infra*.

Pharmaceutically acceptable salts and their preparation are well known to those skilled in pharmaceuticals. Pharmaceutically acceptable salts of the compounds of Formula (I) or Formula (II) which are useful in the present invention include, but are not limited to, maleate, fumarate, lactate, oxalate, methanesulfonate, ethane-sulfonate, benzenesulfonate, tartrate, citrate, hydrochloride, hydrobromide, sulfate and phosphate salts. Preferred pharmaceutically acceptable salts of the compounds of Formula (I) or Formula (II) include hydrochloride and hydrobromide salts, and such salts can be

- 19 -

prepared by known techniques such as the method of Bender et al., U.S. Patent 4,175,127, the disclosure of which is hereby incorporated by reference.

Preferred compounds of Formula (IA) include those wherein:

W is $-\text{CR}_5=\text{CR}_7-$, $-\text{N}=\text{CR}_7-$, $-\text{S}(\text{O})_m-$ or $-\text{O}-$;

one of R_1 and R_0 is 4-pyridyl or C_{1-2} alkyl-4-pyridyl, provided that when R_1 is C_{1-2} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

(a) monosubstituted phenyl wherein said substituent is C_{1-2} alkylthio, C_{1-2} alkylsulfinyl, C_{2-3} 1-alkenyl-1-thio, 2-propenyl-1-thio, 1-acyloxy-1-alkylthio, C_{1-2} alkoxy, halo; or

(b) disubstituted phenyl wherein said substituents are, independently, C_{1-2} alkylthio or C_{1-2} alkoxy; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-2} alkylsulfinyl, C_{2-3} 1-alkenyl-1-thio, 2-propenyl-1-thio or 1-acyloxy-1-alkylthio and the other is C_{1-2} alkoxy; or

(d) disubstituted phenyl wherein the substituents are the same and are C_{1-2} alkylsulfinyl, C_{2-3} 1-alkenyl-1-thio, 2-propenyl-1-thio or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group;

provided that:

(1.) when W is $-\text{CR}_5=\text{CR}_7-$ or $-\text{N}=\text{CR}_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are -H;

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is $\text{S}(\text{O})_m$;

m is 0, 1 or 2;

n is 1 or 2;

R_3 and R_9 are -H; and

R_2 and R_8 are -H; then

one of R_1 or R_0 is 4-pyridyl, and the other of R_1 and R_0 is:

(a) monosubstituted phenyl wherein said substituent is selected from C_{2-3} 1-alkenyl-1-thio, 2-propenyl-1-thio or 1-acyloxy-1-alkylthio; or

(b) disubstituted phenyl wherein said substituents are C_{1-2} alkylthio; or

- 20 -

(c) disubstituted phenyl wherein one of said substituents must be C₁₋₂ alkylthio, C₁₋₂ alkylsulfinyl, C₂₋₃ 1-alkenyl-1-thio, 2-propenyl-1-thio or 1-acyloxy-1-alkylthio and the other is C₁₋₂ alkoxy; and

(3.) when W is S(O)_m;

5

m is 0;

n is 1; and

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; then

R₃ and R₉ are, -H; and

1 0 (4.) when W is -O- then

n is 1;

R₃ and R₉ are -H; and

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring.

1 5

The most preferred compound of Formula (IA) is 2-(4-methoxyphenyl)-3-(4-pyridyl)-imidazo[1,2-a]-pyridine.

Preferred compounds of Formula (I) include those wherein:

2 0

W₁ is -(CR₄R₅)-(CR₆R₇)-, -CR₅=CR₇-, or -S(O)_m;

one of R₁ and R₀ is 4-pyridyl or C₁₋₂ alkyl-4-pyridyl, provided that when R₁ is C₁₋₂ alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R₁ and R₀ is:

2 5

(a) monosubstituted phenyl wherein said substituent is C₁₋₂ alkylthio, C₁₋₂ alkylsulfinyl, 1-acyloxy-1-alkylthio, C₁₋₂ alkoxy or halo, or

(b) disubstituted phenyl wherein said substituents are, independently, C₁₋₂ alkylthio or C₁₋₂ alkoxy, or

(c) disubstituted phenyl wherein one of said substituents is C₁₋₂ alkylsulfinyl or 1-acyloxy-1-alkylthio and the other is C₁₋₂ alkoxy, or

3 0

(d) disubstituted phenyl wherein the substituents are the same and are C₁₋₂ alkylsulfinyl or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group;

provided that:

(1.) when W₁ is -(CR₄R₅)-(CR₆R₇)- then

3 5

n is 0 or 1; and

R₂, R₃, R₄, R₅, R₆, R₇, R₈, and R₉ are -H; and

when R₁ or R₀ is 4-pyridyl, the other of R₁ and R₀ is other than mono-C₁₋₂ alkoxy-substituted phenyl or mono-halo-substituted phenyl;

- 21 -

when n is 0, R₄ and R₅ together are oxo; R₄ and R₅ may both be fluoro, or one of R₄ and R₅ is H and the other is OH;

(2.) when W₁ is -CR₅=CR₇- then

n is 1;

5 R₃, R₅, R₇ and R₉ are -H; and

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic pyridine ring;

(3.) when W₁ is S(O)_m then

m is 0, 1 or 2;

10 n is 1 or 2; and

R₃ and R₉ are -H;

R₂ and R₈ are -H or R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring;

further provided that:

15 (a) when R₂ and R₈ are -H and R₁ or R₀ is 4-pyridyl, then the other of R₁ and R₀ is other than mono-C₁₋₂ alkoxy-substituted phenyl or mono-halo-substituted phenyl; and

(b) when R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring, then m is 0 and n is 1; and

20

(4) when W₁ is -O- then

n is 1;

R₃ and R₉ are -H; and

25

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring.

Especially preferred compounds of Formula (I) having superior IL-1 inhibiting activity include the following:

2-(4-methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;

30

2-(4-methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;

2-(4-ethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;

35

2-(4-ethylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;

2-(4-methylthiophenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;

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- 2-(4-methylsulfinylphenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
- 2-(4-methoxyphenyl)-3-(4-pyridyl)-imidazo[1,2-a]-pyridine;
- 5 5-(3,4-(methylenedioxy)phenyl)-6-(4-pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole;
- 2-(4-methoxyphenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;
- 2-(4-acetoxymethylthiophenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole.
- 10 2-(trimethylacetylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
- 6-(4-methylthiophenyl)-5-(4-pyridyl)-2,3-dihydro-imidazo[2,1-b]-thiazole;
- 5-(4-methylthiophenyl)-6-(4-pyridyl)-2,3-dihydro-imidazo-
- 15 [2,1-b]-thiazole;
- 3-(4-methylthiophenyl)-2-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
- 2-(4-propylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]-imidazole;
- 20 2-(4-methylthiophenyl)-3-(4-(2-ethyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole;
- 2-(4-Mercaptophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]-imidazole disulfide;
- 25 2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-[7H]-pyrrolo[1,2-a]-imidazole;
- 5,6-dihydro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole-7-ol; and
- 5,6-dihydro-7,7-difluoro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole.

30

Preferred compounds useful in the method of inhibition of the production of TNF of the subject invention include those compounds of Formula (II) wherein:

- 35 W_1 is $-(CR_4R_5)-(CR_6R_7)-$, $-CR_5=CR_7-$, or $-S(O)_m-$;
- one of R_1 and R_0 is 4-pyridyl or C_{1-2} alkyl-4-pyridyl, provided that when R_1 is C_{1-2} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

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(a) monosubstituted phenyl wherein said substituent is C₁₋₂ alkylthio, C₁₋₂ alkylsulfinyl, 1-acyloxy-1-alkylthio, C₁₋₂ alkoxy or halo, or

5 (b) disubstituted phenyl wherein said substituents are, independently, C₁₋₂ alkylthio or C₁₋₂ alkoxy, or

(c) disubstituted phenyl wherein one of said substituents is C₁₋₂ alkylsulfinyl or 1-acyloxy-1-alkylthio and the other is C₁₋₂ alkoxy, or

1 0 (d) disubstituted phenyl wherein the substituents are the same and are C₁₋₂ alkylsulfinyl or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group;

provided that:

(1.) when W₁ is -(CR₄R₅)-(CR₆R₇)- then

n is 0;

1 5 and R₄ and R₅ may together form an oxo; R₄ and R₅ are both fluoro; or one of R₄ and R₅ is H and the other OH; or

(2.) when W₁ is -CR₅=CR₇- or -N=CR₇- then

n is 1;

2 0 R₃, R₅, R₇ and R₉ are, independently, -H or C₁₋₂ alkyl; and

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring;

(3.) when W₁ is S(O)_m then

2 5 m is 0, 1 or 2;

n is 1 or 2; and

R₃ and R₉ are, independently, -H or C₁₋₂ alkyl;

3 0 R₂ and R₈ are, independently, -H or C₁₋₂ alkyl or R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring;

further provided that:

(a) when R₂ and R₈ are, independently, -H or C₁₋₂ alkyl and R₁ or R₀ is 4-pyridyl, then the other of R₁ and R₀ mono-fluoro-substituted phenyl; and

3 5 (b) when R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring, then m is 0 and n is 1; and

(4.) when W₁ is -O- then

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n is 1; R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; and
 R₂ and R₈ together represent a double bond in the B ring such that the
 B ring is an aromatic oxazole ring;
 or a pharmaceutically acceptable salt thereof.

5

Additional preferred compounds of Formula (II) are when

(1.) when W₁ is -(CR₄R₅)-(CR₆R₇)-;

1 0 n is 0; and R₂ and R₈ are, independently, -H or C₁₋₂ alkyl
 and R₁ or R₀ is 4-pyridyl or C₁₋₄alkyl-4-pyridyl, then the other of
 R₁ and R₀ is a mono-C₁₋₃alkylthio, C₁₋₃ alkylsulfinylphenyl or a
 mono-halo-substituted phenyl;

(2) when W₁ is S(O)_m;

1 5 m is 0, 1 or 2; n is 1 or 2; and R₂ and R₈ are, independently, -H or
 C₁₋₂ alkyl and R₁ or R₀ is 4-pyridyl, then the other of R₁ and R₀ is
 other than mono-fluoro-substituted phenyl.

Especially preferred compounds for use in the method of the subject
 invention for inhibition of TNF production are

- 2-Phenyl-3-pyridyl-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole;
 2-4-Bromophenyl-3-pyridyl-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole;
 2 0 2-(4-Methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-
 imidazole;
 2-(4-Fluorophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-
 imidazole;
 3-(4-Fluorophenyl)-2-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-
 2 5 imidazole;
 2-(4-Pyridyl)-3-(4-methylthiophenyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-
 imidazole;
 2-(4-Methylthiophenyl)-3-[4-(2-methylpyridyl)]-6,7-dihydro-[5H]-
 pyrrolo[1,2-a]-imidazole;
 3 0 2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-7H-pyrrolo-
 [1,2-a]imidazole;
 5,6-Dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-[7H]-pyrrolo-[1,2-a]-
 imidazole-7-ol;
 2-(4-Acetoxymethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-
 3 5 [1,2-a]-imidazole;
 2-(4-Methoxyphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-
 [1,2-a]imidazole;
 2-(4-Methylsulfoxyphenyl)-3-(4-pyridyl)-6,7-dihydro[5H]-pyrrolo-

[1,2-a]imidazole;

2-(4-Ethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole; or

5 2-(4-Ethylsulfonylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.

Also found to possess inhibition of TNF production are the following compounds, which are useful in the process of using this invention:

6-(4-Fluorophenyl)-5-(4'-pyridyl)-2,3-dihydroimidazo-[2,1-b]thiazole-1-oxide;

1 0 6-(4-Fluorophenyl)-5-(4-pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole-1,1-dioxide; or

5-(4-Fluorophenyl)-6-(4'-pyridyl)-2,3-dihydroimidazo-[2,1-b]thiazole.

1 5 Interleukin-1 (IL-1) has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and
2 0 the suppression of plasma iron levels.

The discovery of a compound which specifically inhibits IL-1 production will not only contribute to the understanding of how this molecule is synthesized, processed and secreted, but will also provide a therapeutic approach for diseases in which excessive or unregulated IL-1 production is implicated.

2 5 It has now been discovered that compounds of Formula (I) and Formula (II) and their pharmaceutically acceptable salts thereof, are useful for inhibiting the production of IL-1 and TNF by monocytes and/or macrophages in a human in need of such inhibition. It should be noted that the compounds of Formula (I) and Formula (II) wherein R₁ or R₀ is a phenyl substituted by a C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-sulfinyl, or C₂₋₅ 2-alkenyl-1-sulfinyl group are prodrugs which are reductively
3 0 converted in vivo to the corresponding alkylthio or alkenylthio form.

There are several disease states in which excessive or unregulated IL-1 production by monocytes and/or macrophages is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis [See, e.g., Fontana et al., Arthritis Rheum., 22, 49-53 (1982)]; osteoarthritis [See, e.g., Wood et al., Arthritis Rheum., 26, 975 (1983)]; endotoxemia and/or toxic shock syndrome [See, e.g., Ikejima and Dinarello, J. Leukocyte Biology, 37, 714 (1985)]; other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin

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- [See, e.g., Habicht and Beck, *J. Leukocyte Biology*, **37**, 709 (1985)]; and inflammatory bowel disease [See, e.g., Satsangi et al., *Clin. Exp. Immunol.*, **67**, 594-605 (1987)]; other chronic inflammatory disease states such as tuberculosis. [See, e.g., Chesque et al., *J. Leukocyte Biology*, **37**, 690 (1985)]; atherosclerosis [See, e.g., Albrightson et al., *J. Immunol.*, **135**, 1872-1877 (1985)]; muscle degeneration [See, e.g., Baracos et al., *N. Eng. J. Med.*, **308**, 553-558 (1983)]; and cachexia [See, e.g., Beutler et al., *J. Immunol.*, **135**, 3969-3971 (1985)]. Benjamin et al., "Annual Reports in Medicinal Chemistry - 20", Chapter 18, pages 173-183 (1985), Academic Press, Inc., disclose that excessive IL-1 production is implicated in: Psoriatic arthritis, Reiter's syndrome, Rheumatoid arthritis, Osteoarthritis, Gout, Traumatic arthritis, Rubella arthritis, and Acute synovitis.

- Dinareello, J. *Clinical Immunology*, **5** (5), 287-297 (1985), reviews the biological activities which have been attributed to IL-1 and such activities are summarized in Table A. It should be noted that some of these effects have been described by others as indirect effects of IL-1.

Table ABiological Activities Attributed to IL-1

	Fever (in rabbits, mice and rats)
	Hypoferremia
2 0	Hypozincemia
	Hypercupremia
	Increased
	Blood neutrophils
	Hepatic acute-phase proteins
2 5	Bone resorption
	Cartilage breakdown
	Muscle proteolysis
	Slow-wave sleep
	Endothelial procoagulant
3 0	Chondrocyte proteases
	Synovial collagenase
	Endothelial neutrophil adherence
	Neutrophil degranulation
	Neutrophil superoxide
3 5	Interferon production
	Proliferation of
	Fibroblasts
	Glial cells

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Table ABiological Activities Attributed to IL-1, cont.

	Mesangial cells
	Synovial fibroblasts
5	EBV B-cell lines
	Chemotaxis of
	Monocytes
	Neutrophils
	Lymphocytes
10	Stimulation of PGE ₂ in
	Hypothalamus
	Cortex
	Skeletal muscle
15	Dermal fibroblast
	Chondrocyte
	Macrophage/monocyte
	Endothelium (PGI ₂)
	Decreased
	Hepatic albumin synthesis
20	Appetite
	Brain binding of opioids
	Augmentation of
	T-cell responses
	B-cell responses
25	NK activity
	IL-2 production
	Lymphokine production

30 An effective, IL-1 production inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof is useful in treating, prophylactically or therapeutically, any disease state in a human which is exacerbated or caused by excessive or unregulated IL-1 production by such human's monocytes and/or macrophages.

35 This invention relates to the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of prophylactically or therapeutically, any disease state in a human which is exacerbated or caused by excessive or unregulated IL-1 or production by such human's monocytes and/or macrophages.

The discovery of a compound which specifically inhibits TNF production will not only contribute to the understanding of how this molecule is synthesized, processed and secreted, but will also provide a therapeutic approach for diseases in which excessive or unregulated TNF production is implicated.

- 5 There are several disease states in which excessive or unregulated TNF production by monocytes and/or macrophages is implicated in exacerbating and/or causing the disease. These include endotoxemia and/or toxic shock syndrome [See Tracey et al., Nature 330:662-664 (1987); Badger et al., Circ. Shock, 27:51-61 (1989) and Hinshaw et al., Circ. Shock 30:279-292 (1990)]; cachexia [See, Dezube et al., 10 Lancet, 335 (8690):662 (1990)]; Adult Respiratory Distress Syndrome where TNF concentration in excess of 12,000 pg/ml have been detected in pulmonay aspirates from ARDS patients. [See, Millar et al., Lancet 2(8665):712-714 (1989). Systemic infusion of recombinant TNF resulted in changes typically seen in ARDS [See, Ferrai-Baliviera et al., Arch. Surg. 124(12):1400-1405 (1989)]; AIDS viral replication of latent HIV in 15 T-cell and macrophage lines can be induced by TNF [See, Folks et al., PNAS 86:2365-2368 (1989)]. A molecular mechanism for the virus inducing activity is suggested by TNF's ability to activate a gene regulatory protein (NF-kB) found in the cytoplasm of cells, which promotes HIV replication through binding to a viral regulatory gene sequence (LTR) [See, Osborn et al., PNAS 86:2336-2340 (1989)]. 20 TNF in AIDS associated cachexia is suggested by elevated serum TNF and high levels of spontaneous TNF production in peripheral blood monocytes from patients [See, Wright et al., J. Immunol. 141(1):99-104 (1988)]. TNF in Bone Resorption Diseases, including arthritis, wherein it has been determined that when activated, leukocytes will produce a bone-reasorbing activity, and data suggests that TNF-a and TNF-β both 25 contribute to this activity. [See e.g., Bertolini et al., Nature 319:516-518 (1986) and Johnson et al., Endocrinology 124(3):1424-1427(1989)] It has been determined that TNF stimulates bone resorption and inhibits bone formation in vitro and in vivo through stimulation of osteoclast formation and activation combined with inhibition of osteoblast function. Although TNF may be involved in may bone resorption disease, 30 including arthritis, the most compelling link with disease is the association between production of TNF by tumor or host tissues and malignancy associated hypercalcemia [See, Calci. Tissue Int. (US) 46(Suppl.):S3-10 (1990)]. In Graft versus Host Reaction, increased serum TNF levels have been associated with major complication following acute allogenic bone marrow transplants [See, Holler et al., Blood, 35 75(4):1011-1016(1990)]; cerebral malaria, which is a lethal hyperacute neurological syndrome associated with high blood levels of TNF and is the most severe complication occuring in malaria patients. A form of experimental cerebral malaria (ECM) that reproduces some features of the human disease was prevented in mice by

administration of an anti-TNF antibody. [See, Grau et al., Imm. Review 112:49-70 (1989)]. Levels of serum TNF correlated directly with the severity of disease and prognosis in patients with acute malaria attacks [See Grau et al., N. Engl. J. Med. 320(24):1586-1591 (1989)]. Another disease state in which TNF plays a role is the area of chronic Pulmonary Inflammatory Disease. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibody to TNF completely blocked the silica-induced lung fibrosis in mice [See Piguet et al., Nature, 344:245-247 (1990)]. High levels of TNF production (in the serum and in isolated macrophages) have been demonstrated in animal models of silica and asbestos induced fibrosis [See Bissonnette et al., Inflammation 13(3):329-339 (1989)]. Alveolar macrophages from pulmonary sarcoidosis patients have also been found to spontaneously release massive quantities of TNF as compared with macrophages from normal donors [See Baughman et al., J. Lab. Clin. Med. 115(1):36-42 (1990)]; TNF is also implicated in another acute disease state such as the inflammatory response which follows reperfusion, called Reperfusion Injury and is a major cause of tissue damage after loss of blood flow. [See, Vedder et al., PNAS 87:2643-2646 (1990)]; TNF also alters the properties of endothelial cells and has various pro-coagulant activities, such as producing an increase in tissue factor pro-coagulant activity and suppression of the anticoagulant protein C pathway as well as down-regulating the expression of thrombomodulin [See, Sherry et al., J. Cell Biol. 107:11269-1277 (1988)]. TNF also has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNF-induced expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells [See, Munro et al., Am. J. Path. 135(1):121-132 (1989)].

TNF is also believed to be an important mediator of many other inflammatory states or diseases. Therefore, inhibitors of TNF production would have utility in any inflammatory state or disease in which abnormal levels of TNF are produced. Abnormal levels of TNF constitute levels of 1) free (not cell bound) TNF, greater than or equal to 1 picogram per.ml; 2) any cell associated TNF; or 3) the presence of TNF mRNA above basal levels in cells or tissues in which TNF is produced. In addition, the present invention attributes many biological disease states noted herein to IL-1 activity. These disease states are also considered appropriate disease states of TNF activity and hence compounds of Formula (II) are also useful in their treatment as well, and should not be considered solely a limitation to IL-1 activity alone.

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An effective, TNF production inhibiting amount of a compound of Formula (II) or a pharmaceutically acceptable salt thereof is useful in treating, prophylactically or therapeutically, any disease state in a human which is exacerbated or caused by excessive or unregulated TNF production by such human's monocytes and/or macrophages.

This invention relates to the use of a compound of Formula (II), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of prophylactically or therapeutically, any disease state in a human which is exacerbated or caused by excessive or unregulated TNF production by such human's monocytes and/or macrophages.

This invention further relates to a compound of Formula (II) for use as a medicament in the treating, prophylactically or therapeutically, any disease state in a human which is exacerbated or caused by excessive or unregulated TNF production by such human's monocytes and/or macrophages.

This invention also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (IA) and a pharmaceutically acceptable carrier or diluent. The compounds of Formula (I) or (II) are administered in conventional dosage forms prepared by combining a compound of Formula (I) or (II) in an amount sufficient to produce IL-1 or TNF production inhibiting activity, respectively, with standard pharmaceutical carriers according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 1 g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

To obtain a stable water soluble dose form of an insoluble Formula (I) compound, a pharmaceutically acceptable salt of the Formula (I) or (II) compound is dissolved in an aqueous solution of an organic or inorganic acid, such as a 0.3 M solution of succinic acid or, preferably, citric acid.

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The method of the subject invention may be carried out by delivering the monokine activity interfering agent parenterally. The term 'parenteral' as used herein includes intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques.

A suitable dose of any TNF production inhibiting compound of a compound of Formula (II) administered parenterally will preferably be from about 1 to about 100 mg per kilogram (kg) of total body weight, most preferably from about 5 to about 80 mg/kg per day. A suitable IL-1 production inhibiting compound of Formula (I) administered parenterally will preferably be from about 1 to about 100 mg per kilogram (kg) of total body weight, preferably from about 5 to about 80mg/kg/day. Most preferably from about 3 to about 60 mg/kg per day. Preferably, each parenteral dosage unit will contain the active ingredient [i.e., the compound of Formula (I) or (II)] in an amount from about 50 mg. to about 500 mg.

The compounds of Formula (I) or Formula (II) may also be administered topically. Thus, the compounds of Formula (I) or Formula (II) may be administered topically in the treatment or prophylaxis of inflammatory topical disease states mediated or exacerbated by excessive IL-1 or TNF production, respectively, such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, inflamed joints, eczema, psoriasis or other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

The amount of a compound of Formula (I) or Formula (II) required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the inflammatory condition and the animal undergoing treatment, and is ultimately at the discretion of the physician. A suitable dose for anti-inflammatory activity for a compound of Formula (I) is 1mg to 100mg. A suitable dose of a compound of Formula (II) for anti-inflammatory activity is 1mg to 1000mg.

By topical administration is meant non-systemic administration and includes the application of a compound of Formula (I) or (II) externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

A suitable dose of an IL-1 production inhibiting compound of Formula (I) is 15 mg to 500 mg of base for topical administration, the most preferred

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dosage being 1 mg to 100 mg, for example, 5 to 25 mg administered two or three times daily. The daily topical dosage regimen will preferably be from about 2 mg to about 10 mg per site of administration.

- 5 A suitable dose of any TNF production inhibiting compound of Formula (II) is from about 1 mg to about 1000 mg of base for topical administration, the most preferred daily dosage being 15 mg to 500 mg, the single dosage range being about 5mg to 160 mg. The daily topical dosage regimen will preferably be two or three times daily.

- 10 While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

- 15 The topical formulations of the present invention comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The present invention also relates to a pharmaceutical composition
20 comprising an effective amount of a compound of Formula (I) or Formula (II) in a pharmaceutically acceptable carrier or diluent with an effective amount of one or more additional agents having IL-1 inhibitory activity, TNF inhibitory activity, cyclooxygenase inhibitory activity or 5-lipoxygenase inhibitory activity .

- 25 Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

- 30 Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C. for half
35 an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents

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for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

5 Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

10 Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of
15 natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or macrogols. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums,
20 cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

 The compounds of Formula (I) or (II) may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or
25 a metered dose inhaler, may be prepared by conventional techniques. The preferred daily dosage amount of a compound of Formula (I) administered by inhalation is from about 1 mg to about 1000 mg per day, preferably from about 1mg to about 100mg per day.

30 A suitable dose of any TNF production inhibiting compound of Formula (II) administered by inhalation is from about 1 mg to about 1000 mg per day. More preferably from about 10mg to about 100mg per day.

 This invention also relates to a method of inhibiting the production of IL-1 by monocytes and/or macrophages in a human in need thereof which comprises administering an effective, IL-1 production inhibiting amount of a compound of
35 Formula (I) or a pharmaceutically acceptable salt thereof to such human. A compound of Formula (I) or a pharmaceutically acceptable salt thereof can be administered to such human in a conventional dosage form prepared by combining a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with a conventional pharmaceutically

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acceptable carrier or diluent according to known techniques, such as those described above as well as those described in Adams et al., U.S.S.N. 255,816 filed October 11, 1988 the disclosure of which is hereby incorporated by reference. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables.

5 A compound of Formula (I) or a pharmaceutically acceptable salt thereof is administered to a human in need of inhibition of IL-1 production by its monocytes and/or macrophages in an amount sufficient to inhibit such excessive IL-1 production to the extent that it is regulated down to normal levels. A compound of Formula (II) or a pharmaceutically acceptable salt thereof is administered to a human in need of inhibition of TNF production by its monocytes and/or macrophages in an amount sufficient to inhibit such excessive TNF production to the extent that it is regulated down to normal levels.

1 5 The route of administration may be oral, parenteral or topical. The term parenteral as used herein includes intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred.

2 0 As stated above, the method of the subject invention may be carried out by delivering the compounds of Formula (I) or (II) orally. Appropriate dosage forms for such administration may be prepared by conventional techniques. A suitable dose of a compound of Formula (I) or (II) for a daily oral dosage regimen will preferably be from about 1 to about 100 mg/kilogram of total body weight, more preferably from about 5mg to 80mg/kg.

2 5 The daily parenteral dosage regimen for a compound of Formula (I) or (II) will preferably be from about 2 to about 80 mg per kilogram (kg) of total body weight, most preferably from about 3 to about 60 mg/kg. The daily topical dosage regimen for a compound of Formula (I) or (II) will preferably be from about 2 mg to about 10 mg per site of administration. It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or (II) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

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EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a
5 limitation of the scope of the present invention in any way.

PHARMACEUTICAL COMPOSITION EXAMPLESEXAMPLE A - CAPSULE COMPOSITION

1 0 A pharmaceutical composition of this invention in the form of a capsule is prepared by filling a standard two-piece hard gelatin capsule with 50 mg. of a compound of Formula (IA), in powdered form, 110 mg. of lactose, 32 mg. of talc and 8 mg. of magnesium stearate.

1 5 EXAMPLE B - INJECTABLE PARENTERAL COMPOSITION

A pharmaceutical composition of this invention in a form suitable for administration by injection is prepared by stirring 1.5% by weight of a compound of Formula (IA) in 10% by volume propylene glycol and water. The solution is sterilized by filtration.

2 0 EXAMPLE C - OINTMENT COMPOSITION

Compound of Formula (IA) 1.0 g
White soft paraffin to 100.0 g

2 5 The compound of Formula (IA) is dispersed in a small volume of the vehicle and this dispersion is gradually incorporated into the bulk to produce a smooth, homogeneous product which is filled into collapsible metal tubes.

EXAMPLE D - TOPICAL CREAM COMPOSITION

Compound of Formula (IA) 1.0 g
3 0 Polawax GP 200 20.0 g
Lanolin Anhydrous 2.0 g
White Beeswax 2.5 g
Methyl hydroxybenzoate 0.1 g
Distilled Water to 100.0 g

3 5 The polawax, beeswax and lanolin are heated together at 60°C and added to a solution of methyl hydroxybenzoate. Homogenization is achieved using high speed stirring and the temperature is allowed to fall to 50°C. The compound of

Formula (IA) is added and dispersed throughout, and the composition is allowed to cool with slow speed stirring.

EXAMPLE E - TOPICAL LOTION COMPOSITION

- 5 Compound of Formula (IA) 1.0 g
Sorbitan Monolaurate 0.6 g
Polysorbate 20 0.6 g
Cetostearyl Alcohol 1.2 g
Glycerin 6.0 g
10 Methyl Hydroxybenzoate 0.2 g
Purified Water B.P. to 100.00 ml

The methyl hydroxybenzoate and glycerin are dissolved in 70 ml of the water at 75°C. The sorbitan monolaurate, polysorbate 20 and cetostearyl alcohol are melted together at 75°C and added to the aqueous solution. The resulting emulsion is
15 homogenized, allowed to cool with continuous stirring and the compound of Formula (IA) is added as a suspension in the remaining water. The whole suspension is stirred until homogenized.

EXAMPLE F - EYE DROP COMPOSITION

- 20 Compound of Formula (IA) 0.5 g
Methyl Hydroxybenzoate 0.01 g
Propyl Hydroxybenzoate 0.04 g
Purified Water B.P. to 100.00 ml

The methyl and propyl hydroxybenzoates are dissolved in 70 ml
25 purified water at 75°C and the resulting solution is allowed to cool. The compound of Formula (IA) is then added, and the solution is made up to 100 ml with purified water. The solution is sterilized by filtration through a membrane filter (0.22 μ m pore size) and packed aseptically into suitable sterile containers.

EXAMPLE G - COMPOSITION FOR ADMINISTRATION BY INHALATION

- 30 For an aerosol container with a capacity of 15-20
ml: Mix 10 mg of a compound of Formula (IA) with 0.1-0.2% of a lubricating agent, such as Span 85 or oleic acid, and disperse such mixture in a propellant (c.a.), such as freon, preferably a combination of freon 114 and freon 12, and put into an appropriate
35 aerosol container adapted for either intranasal or oral inhalation administration.

EXAMPLE H - COMPOSITION FOR ADMINISTRATION BY INHALATION

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For an aerosol container with a capacity of 15-20 ml: Dissolve 10 mg of a compound of Formula (IA) in ethanol (6-8 ml), add 0.1-0.2% of a lubricating agent, such as Span 85 or oleic acid, and disperse such in a propellant (c.a.), such as freon, preferably a combination of freon 144 and freon 12, and put into an appropriate aerosol container adapted for either intranasal or oral inhalation administration.

UTILITY EXAMPLES

In Tables 1 and 2 of the following Utility Examples, the following abbreviations are employed:

	<u>ABBREVIATION</u>	<u>FORMULA (I) COMPOUND</u>
1 0	Compound 1	2-(4-methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
	Compound 2	2-(4-methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
1 5	Compound 3	2-(4-ethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
	Compound 4	2-(4-ethylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
2 0	Compound 5	2-(4-methylthiophenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
	Compound 6	2-(4-methylsulfinylphenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
	Compound 7	2-(4-methoxyphenyl)-3-(4-pyridyl)-imidazo-[1,2-a]-pyridine.
2 5	Compound 8	5-(3,4-(methylenedioxy)phenyl)-6-(4-pyridyl)-2,3-dihydroimidazo-[2,1-b]-thiazole.
	Compound 9	2-(4-methoxyphenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
3 0	Compound 10	2-(4-acetoxymethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
	Compound 11	6-(4-methylthiophenyl)-5-(4-pyridyl)-2,3-dihydro-imidazo-[2,1-b]-thiazole.
	Compound 12	5-(4-methylthiophenyl)-6-(4-pyridyl)-2,3-dihydro-imidazo-[2,1-b]-thiazole.
3 5	Compound 13	3-(4-methylthiophenyl)-2-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.

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Compound 14	2-(4-propylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
Compound 15	2-(4-methylthiophenyl)-3-(4-(2-ethylpyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.

5

EXAMPLE A

Inhibitory Effect of compounds of Formula (I) on in vitro IL-1 Production by Human Monocytes

1 0 The effects of compounds of Formula (I) on the in vitro production of IL-1
by human monocytes was examined using the following protocol.

 Bacterial lipopolysaccharide (LPS) was used to induce IL-1 production by
human peripheral blood monocytes. IL-1 activity was measured by its ability to
stimulate a Interleukin 2 (IL-2) producing cell line (EL-4) to secrete IL-2, in concert
1 5 with A23187 ionophore, according to the method of Simon et al., J. Immunol.
Methods, 84, 85, (1985). Human peripheral blood monocytes were isolated and
purified from either fresh blood preparations from volunteer donors, or from blood
bank buffy coats, according to the procedure of Colotta et al., J. Immunol., 132, 936
(1984). 1×10^6 of such monocytes were plated in 24-well plates at a concentration of
2 0 1-2 million/ml per well. The cells were allowed to adhere for 2 hours, after which time
non-adherent cells were removed by gentle washing. Test compounds were then added
to the cells for 1 hour (hr) before the addition of lipopolysaccharide (50 ng/ml), and the
cultures were incubated at 37°C for an additional 24 hours. At the end of the
incubation period, culture supernatants were removed and clarified of cells and all
2 5 debris. Culture supernatants were immediately assayed for IL-1 biological activity in
the manner described above, as well as for prostaglandin and/or leukotriene
concentrations by radioimmunoassay.

 The results indicated that human peripheral blood monocytes are exquisitely
sensitive to bacterial endotoxin. Nanogram or even picogram quantities of LPS
3 0 stimulated high levels of IL-1 production as well as prostaglandin production; however,
little, if any, leukotriene was detected in such supernatants. These observations are
consistent with previous reports [(See, Humes et al., J. Biol. Chem., 257, 1591
(1982)].

 The results of the effects of compounds of Formula (I) on the in vitro
3 5 IL-1 production by human monocytes is reported in Table 1. As shown in Table 1,
compounds of Formula (I), other than those compounds wherein R is a sulfinyl
derivative, are potent inhibitors of in vitro IL-1 production by human monocytes. As
shown in Table 1, the sulfinyl derivatives are not active in the in vitro assay. In fact,

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the sulfinyl derivatives of Formula (I) possess no known biological activity in any in vitro assay. However, the sulfinyl derivatives function as prodrugs to their corresponding sulfide, i.e., they function in vivo to inhibit the production of IL-1 because they are metabolized so that they are reductively converted, in vivo, to their corresponding biologically active alkylthio or alkenylthio form. Proof of this in vivo conversion of the sulfinyl derivatives to a biologically active form is indicated by the antiinflammatory activity of the sulfinyl compounds in the in vivo assay described in Table 2.

-40-

TABLE 1

EFFECT OF COMPOUNDS OF FORMULA (I) ON LPS-STIMULATED IL-1
PRODUCTION BY HUMAN MONOCYTES^b

5	<u>COMPOUND NUMBER</u>	<u>IC₅₀(uM)</u>
	1	2.0
	2	NA ^a
	3	2.0
	4	NA
10	5	2.7
	6	NA
	7	1.0
	8	10.0
	9	0.7
15	10	6.3
	11	1.8
	12	1.8
	13	2.0
	14	>10.0
20	15	1.3

^a NA means not active

^b IL-1 activity was assayed as described above, i.e., by culturing EL4 cells with
25 dilutions of supernatant from monocytes and subsequently culturing EL4 supernatants
on a IL-2 dependent cell line.

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TABLE 2
ANTIINFLAMMATORY ACTIVITY OF THE SULFINYL
DERIVATIVES OF FORMULA (I)

5	COMPOUND NUMBER (50 mg/kg p.o.)	PERCENT INHIBITION OF ARACHIDONIC ACID-INDUCED MOUSE EAR SWELLING ^a
10	1	56***b
	2	44***
	3	56***
	4	41***
	5	59***
	6	59***
15		

^a Mouse ear edema was measured as described in Griswold *et al.*, Inflammation, 11(2), 189-199 (1987), the disclosure of which is hereby incorporated by reference.

^b *** indicates statistical significance at a p less than 0.001

20 The exact mechanism by which any compound of Formula (I) inhibits in vitro IL-1 production by monocytes is not presently known.

25 The data in Table 1 show that compounds of Formula (I) inhibit IL-1 production by human monocytes in vitro. This inhibitory activity does not seem to correlate with the property of any of the compounds of Formula (I) in mediating arachidonic acid metabolism inhibition since other nonsteroidal antiinflammatory drugs with potent cyclooxygenase and/or lipoxygenase inhibitory activity do not inhibit IL-1 production at nontoxic doses. Furthermore, the ability of a compound to inhibit production of prostaglandin and/or leukotriene synthesis does not mean that it will necessarily also inhibit IL-1 production.

30 Based on the widely held belief of the role of unmodulated (i.e., excessive) in vivo IL-1 production in causing or aggravating inflammatory responses and other disease states (see, e.g., Fontana *et al.*, *supra*; Wood *et al.*, *supra*; Akejima and Dinarello, *supra*; Habicht and Beck, *supra*; Chesque *et al.*, *supra*; Benjamin *et al.*, *supra*; and Dinarello, *supra*), and based on the fact that compounds of Formula (I) inhibit in vitro IL-1 production by human macrophages and/or monocytes (see, Table 1), or are converted in vivo to their biologically active form (see, Table 2), all compounds of Formula (I) will inhibit the in vivo IL-1 production by monocytes and/or

macrophages in a human in need thereof when used according to the method of the subject invention.

The inhibitory action of IL-1 activity has not been found to correlate with arachidonic acid metabolism for the compounds of Formula (I). This further substantiates the unpredictable nature of the compounds of Formula (I) for possessing either IL-1.

In Table 3 the following additional compound abbreviations employed are:

1 0	Compound 16	2-[Trimethylacetyl(thiophenyl)]-3-(4-pyridyl)-6,7-dihydro[5H]pyrrolo-[1,2-a]-imidazole.
	Compound 17	2-(4-(2-Propoxy)phenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
	Compound 18	2-(4-(1-Ethoxy)phenyl)-3-(4-pyridyl)-6,7-dihydro[5H]pyrrolo-[1,2-a]-imidazole.
1 5	Compound 19	2-(4-(1-Propoxy)phenyl)-3-(4-pyridyl)-6,7-dihydro[5H]pyrrolo-[1,2-a]-imidazole.
	Compound 20	2-(Acetyl-thio-phenyl)-3-(4-pyridyl)-6,7-dihydro[5H]-pyrrolo-[1,2-a]-imidazole.
	Compound 21	2-(4-Methoxyphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-N-methylimidazole, monomethylsulfate.
2 0	Compound 22	2-Phenyl-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole.
	Compound 23	2-(4-Mercaptophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole disulfide.
	Compound 24	2-(4-Methoxyphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
2 5	Compound 25	6-(4-Methoxyphenyl)-5-(4-pyridyl)-2,3-dihydroimidazo-[2,1-b]-thiazole.
	Compound 26	5-(4-Methoxyphenyl)-6-(4-pyridyl)-2,3-dihydroimidazole-[2,1-b]-thiazole.
	Compound 27	2-(4-Bromophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
3 0		

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TABLE 3Inhibition of IL-1 production by LPS stimulated monocytes in vitro

<u>Compound</u>	
<u>Number</u>	<u>IC₅₀ (mM)</u>
5	
16	NA
17	NA
18	10
19	NA
10	
20	NA
21	NA
22	0.5
23	5.9
24	0.1
15	
25	3.0
26	≥10
27	0.7

 NA =essentially considered not active at 10 mM

20

UTILITY EXAMPLE FOR INHIBITION OF THE PRODUCTION OF TNFEXAMPLE A

Two models of endotoxin shock have been utilized to determine in vivo TNF activity and are described below. The actual protocol used in the models is described in Utility Model Examples A and B set out below, i.e. P. acnes model and LPS-GAL model. In these models protection from the lethal effects of endotoxin shock is provided by the compound 2-(4-methyl-sulfoxyphenyl)-3-(4-pyridyl)-6,7-dihydro[5H]-pyrrolo-[1,2-a]-imidazole (herein called Compound A). The data in Figures 1-5 clearly demonstrates the ability of Compound 1 to reduce the in vivo level of tumor necrosis factor (TNF).

Compound 1 shows a reduction in serum TNF levels in the P acnes/LPS treated mice model as depicted by the data shown in Figure 1, which demonstrates decreased levels of in vivo TNF relative to increased oral dosage of Compound A. Figure 2 demonstrates inhibition of TNF production, also in the P. acnes/LPS Model for Compound A..

Figure 3 shows a reduction of serum TNF levels at 100 mg/kg for Compound A in the LPS-GAL Model. Figure 4 demonstrates 100% survival rate of the animals

with endotoxic shock in the LPS-GAL model after treatment with Compound A compared to only a 30% survival rate of the animals in the control group.

It has also been determined, using one or both of the *in vivo* assays described herein, that 2-(4-Ethylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole, 2-(4-methylthiophenyl)-3-[4-(2-methylpyridyl)]-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole, and 6-(4-Fluorophenyl)-5-(4-pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole-1,1-dioxide also inhibited *in vivo* TNF levels as well as protected the animals from endotoxic induced shock.

The data shown herein demonstrate that the compounds of the present invention inhibit TNF production in a mammal. Therefore, the compounds of the present invention are useful as monokine activity interfering agents, e.g. they are useful in inhibiting the production of tumor necrosis factor (TNF) by monocytes or macrophages in a human.

UTILITY EXAMPLE MODEL A

1 5 Endotoxin Shock in D-gal-Sensitized Mice

The protocol used to test the compound of the method of the subject invention was essentially as has been described in Galanos et al., Proc. Nat'l Acad. Sci USA, 76:5939-43 (1979) whose disclosure is herein incorporated by reference. Briefly, D-gal (D(+) Galactosidase) sensitizes various strains of mice to the lethal effects of endotoxin. The administration of D-gal (300-500mg/kg) intra-venously (i.v.) sensitizes the mice to doses of Lipopolysaccharide(LPS) as low as 0.1mg. Briefly, male C57BL/6 mice, obtained from Charles River Laboratories (Stone Ridge, New York, USA) of 6-12 weeks of age were injected i.v. with 0.1 mg of LPS from Salmonella typhosa (Difco Laboratories, Detroit, Michigan, USA) admixed with D-(+)-gal (Sigma; 500 mg/kg) in 0.20-0.25 ml pyrogen-free saline. Compounds to be tested were administered at various times prior to or following the i.v. injection of LPS/D-gal. In this model, the control animals usually die 5-6 hr. following the injection of LPS, although on occasion deaths are seen between 24 and 48 hr.

UTILITY MODEL EXAMPLE B

3 0 Endotoxin Shock in P. acnes-Sensitized Mice

This model is a modification of the previously described protocol for the *in vivo* induction of TNF as described in Haranaka et al., Cancer Immunol Immunother, 18:87-90, (1984). Treatment with Propionibacterium Acnes (P. acnes) (1mg/animal i.p.) renders mice susceptible to the lethal effects of LPS injected 10 days later.

P. acnes was purchased from Burroughs Wellcome (Triangle Park, North Carolina, USA), and 1 microgram (ug) of the heat-killed bacteria was administered in 0.5 ml pyrogen-free saline by intraperitoneal (i.p.) injection to male C57BL/6 mice, obtained from Charles River Laboratories (Stone Ridge, New York, USA) of 6-12

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weeks of age. Ten days later, the mice were injected i.v. with 1 mg LPS in 0.25 ml saline. Compounds to be tested were administered at various times prior to or following the injection of LPS. The survival of animals was monitored for 1 week.

Measurement of TNF Activity

- 5 Plasma levels of TNF were measured using a modification of the basic sandwich ELISA method described in Winston et al., Current Protocols in Molecular Biology, Pg. 11.2.1, Ausubel et al., Ed. (1987) John Wiley and Sons, New York , USA. The Elisa employed a hamster monoclonal anti-mouse TNF (Genzyme, Boston, MA, USA) as the capture antibody and a polyclonal rabbit anti-murine TNF
- 1 0 (Genzyme, Boston, MA, USA) as the detecting antibody. TNF levels in rat samples were calculated from a standard curve generated with recombinant murine TNF (Genzyme, Boston, MA , USA). TNF levels determined by ELISA correlated with levels detected by the L929 bioassay of Ruff et. al., J. Immunol. 125:1671-1677 (1980), with 1 Unit of activity in the bioassay corresponding to 70 picograms (pg) of
- 1 5 TNF in the ELISA. The ELISA detected levels of TNF down to 25 pg/ml.

UTILITY EXAMPLES

In the following Table B of the Utility Examples, the following abbreviations are employed:

	<u>ABBREVIATION</u>	<u>FORMULA (I) COMPOUNDS</u>
5	Compound A	2-(4-Methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro[5H]-pyrrolo-[1,2-a]imidazole;
	Compound B	2-(4-methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]-imidazole;
10	Compound C	2-phenyl-3-pyridyl-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
	Compound D	2-p-bromophenyl-3-pyridyl-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole;
15	Compound E	2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-7-H-pyrrolo-[1,2-a]imidazole;
	Compound F	5,6-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-[7H]-pyrrolo[1,2-a]-imidazole-7-ol;
20	Compound G	2-(4-Acetoxymethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro[5H]pyrrolo-[1,2-a]-imidazole;
	Compound H	2-(4-Methoxyphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;
25	Compound I	6-(4-Fluorophenyl)-5-(4'-pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole-1-oxide;
30	Compound J	6-(4-Fluorophenyl)-5-(4-pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole-1,1-dioxide;
	Compound K	2-(4-Ethylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro[5H]pyrrolo-[1,2-a]-imidazole;
	Compound L	2-(4-Methylthiophenyl)-3-[4-(2-methylpyridyl)]-6,7-dihydro[5H]pyrrolo-[1,2-a]imidazole.
35	Compound M	2-(4-Fluorophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.

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Compound N

3-(4-Fluorophenyl)-2-(4-pyridyl)-6,7-
dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.

EXAMPLE AInhibitory Effect of Compounds on in vitro TNF Production by Human Monocytes

5 The effects of the compounds enumerated above on the in vitro production of TNF by human monocytes was examined using the following protocol.

 Bacterial lipopolysaccharide (LPS) was used to induce TNF production by human peripheral blood monocytes. TNF activity was measured by a modification of Winston et al., ELISA, described below. Human peripheral blood monocytes were
10 isolated and purified from either fresh blood preparations from volunteer donors, from blood bank buffy coats, or from plateletpheresis residues according to the procedure of Colotta et al., J. Immunol., 132, 936 (1984). 1×10^6 of such monocytes were plated in 24-well plates at a concentration of 1-2 million/ml per well. The cells were allowed to adhere for 2 hours, after which time non-adherent cells were removed by gentle
15 washing. Test compounds were then added to the cells for 1 hour (hr) before the addition of LPS (50 ng/ml), and the cultures were incubated at 37°C for an additional 24 hours. At the end of the incubation period, culture supernatants were removed and clarified of cells and all debris. Culture supernatants were immediately assayed for TNF levels in the manner described below.

20 MEASUREMENT OF HUMAN TNF:

 Levels of TNF were measured using a modification of the basic sandwich ELISA assay method described in Winston et al., Current Protocols in Molecular Biology, Page 11.2.1, Ausubel et al., Ed. (1987) John Wiley and Sons, New York, USA. The Elisa employs a murine monoclonal anti-human TNF antibody, described
25 below, as the capture antibody and a polyclonal rabbit anti-human TNF, described below, as the second antibody. For detection, a peroxidase-conjugated goat anti-rabbit antibody (Boehringer Mannheim, Indianapolis, Indiana, USA, Catalog # 605222) was added followed by a substrate for peroxidase (1mg/ml orthophenylenediamine with 0.1% urea peroxide). TNF levels in samples were calculated from a standard curve
30 generated with recombinant human TNF produced in E. Coli (obtained from SmithKline Beecham Pharmaceuticals, King of Prussia, PA, USA).

PRODUCTION OF ANTI-HUMAN TNF ANTIBODIES:

 Monoclonal antibodies to human TNF were prepared from spleens of BALB/c mice immunized with recombinant human TNF using a modification of the
35 method of Kohler and Millstein, Nature 256:495 (1975), the entire disclosure of which is hereby incorporated by reference. Polyclonal rabbit anti-human TNF antibodies were prepared by repeated immunization of New Zealand White (NZW) rabbits with

recombinant human TNF emulsified in complete Freund's adjuvant (DIFCO, IL., USA).

5 The results indicated that human peripheral blood monocytes are exquisitely sensitive to bacterial endotoxin. Nanogram or even picogram quantities of LPS stimulated high levels of TNF production as well as for IL-1 production.

The results of the effects of compounds on the in vitro TNF production by human monocytes are reported in Table B. The compounds wherein the phenyl substituent group of the pyrrolo[2,1-b]imidazoles and the dihydroimidazo [2,1-a] thiazoles of the present invention are not a sulfinyl derivatives, are potent inhibitors of in vitro TNF production by human monocytes. The compounds wherein the substituent is a sulfinyl derivatives are not active in the in vitro assay. However, the sulfinyl derivatives function as prodrugs to their corresponding sulfide, i.e., they function in vivo to inhibit the production of TNF, because they are metabolized so that they are reductively converted, in vivo, to their corresponding biologically active alkylthio or alkenylthio form. Proof of this in vivo conversion of the sulfinyl derivatives to a biologically active form is indicated by the in vivo activity of the sulfinyl compounds in the in vivo assay described in Utility Models Examples A and B for Compound 2. The conversion of the sulfinyl/sulfoxy pro-drug derivatives to their active sulfinyl structure also holds true for IL-1 activity and is shown herein.

20 The results of the compounds of Formula (II) on the in vitro TNF production by human monocytes are reported in Table B. In Table B, NA = not active.

TABLE B

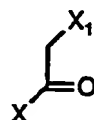
LPS induced TNF Human Monocyte data

<u>Compound No.</u>	<u>IC₅₀ (mM)</u>
25 A (Sulfinyl derivative)	NA
B (Thio derivative)	1.0
C	0.8
D	1.0
E	1.0
30 F	1.0
G	3.0
H	0.5
I	0.2
J	9.0
35 K	7.0
L	7.0
M	0.2
N	1.0

SYNTHESIS EXAMPLES

As more elaborately described herein, all of the compounds of Formulas (C), (D), (E), (F) and (G) are useful as intermediates in the preparation of the compounds of Formula (IA). Additionally, as more elaborately described herein, while all of the compounds of Formula (IA) are useful in the method of the subject invention, some of the compounds of Formula (IA) are also useful as intermediates for preparation other compounds of Formula (IA).

As used herein in the Synthesis Examples, the term "Formula (A)" refers to a compound of the formula:



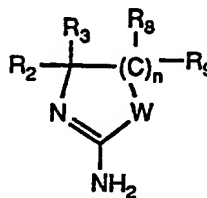
FORMULA (A)

wherein:

X is chosen from a group consisting of mono or disubstituted phenyl, 4-pyridyl and mono-C₁₋₄ alkyl-substituted-4-pyridyl; and

X₁ is a halogen such as Cl or Br.

As used herein in the Synthesis Examples, the term "Formula (B)" refers to a compound of the formula:



FORMULA (B)

wherein:

W is -(CR₄R₅)-(CR₆R₇)-, -(NR₄)-(CR₆R₇)-, S(O)_m or O;

m is 0; and

n is 1 or 2;

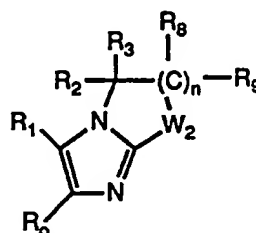
provided that:

(A) when W is -(CR₄R₅)-(CR₆R₇)- or -(NR₄)-(CR₆R₇)- and n is 1; R₂, R₈ and R₄, R₆ together represent two C=C bonds to form an aromatic pyridine ring or an aromatic pyrimidine ring; R₃, R₅, R₇ and R₉ are H or one or more of R₃, R₅, R₇ and R₉ are independently selected from H or C₁₋₂ alkyl;

(B) when W is $S(O)_m$ or O, m is 0 and n is 1; R_3 and R_9 are H or one or more of R_3 and R_9 are independently selected from H or C_{1-2} alkyl; R_2 , R_8 forms a C=C bond in an aromatic thiazole or oxazole ring; or

(C) when W is $S(O)_m$, m is 0, and n is 1 or 2; R_2 , R_3 , R_8 and R_9 are H or one or more of R_2 , R_3 , R_8 and R_9 are independently selected from H or C_{1-2} alkyl.

As used herein in the Synthesis Examples, the term "Formula (Ib)" refers to a compound of the formula:



FORMULA (Ib)

wherein:

W_2 is $-(CR_4R_5)-(CR_6R_7)-$, $-(NR_4)-(CR_6R_7)-$, $S(O)_m$ or O;

m is 0;

n is 1 or 2; and

One of R_1 or R_6 is 4-pyridyl and the other is selected from:

(a) monosubstituted phenyl wherein said substituent is selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, H, or C_{1-4} alkyl; or

(b) disubstituted phenyl wherein said substituents are independently selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl, or the disubstituents together form a methylene dioxy group;

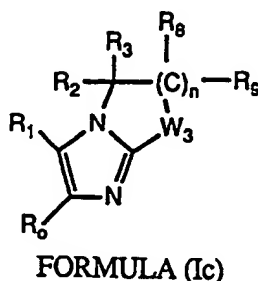
provided that:

(A) when W_2 is $-(CR_4R_5)-(CR_6R_7)-$ or $-(NR_4)-(CR_6R_7)-$ and n is 1; R_2 , R_8 and R_4 , R_6 together represent two C=C bonds to form an aromatic pyridine ring or an aromatic pyrimidine ring; R_3 , R_5 , R_7 and R_9 are H or one or more of R_3 , R_5 , R_7 and R_9 are independently selected from H or C_{1-2} alkyl; or

(B) when W_2 is $S(O)_m$, m is 0, and n is 1 or 2; R_2 , R_3 , R_8 and R_9 are H or one or more of R_2 , R_3 , R_8 and R_9 are independently selected from H or C_{1-2} alkyl; or

(C) when W_2 is $S(O)_m$ or O, m is 0 and n is 1; R_3 and R_9 are H or one or more of R_3 and R_9 are independently selected from H or C_{1-2} alkyl; R_2 , R_8 forms a C=C bond in an aromatic thiazole or oxazole ring.

As used herein in the Synthesis Examples, the term "Formula (Ic)" refers to a compound of the formula:



wherein:

W₃ is -(CR₄R₅)-(CR₆R₇)-, -(NR₄)-(CR₆R₇)-, S(O)_m or O;

m is 0 or 2;

10

n is 1 or 2;

one of R₁ or R₉ is 4-pyridyl or mono-C₁₋₄alkyl-substituted-4-pyridyl, provided that when R₁ is mono-C₁₋₄alkyl-substituted-4-pyridyl the mono-C₁₋₄alkyl substituent is located at the 2-position of the pyridine ring, and the other of R₁ or R₉ is selected from:

15

(a) monosubstituted phenyl wherein said substituent is C₁₋₃ alkylsulfinyl; or

(b) disubstituted phenyl wherein one of said substituents must be C₁₋₃ alkylthio and the other is selected from C₁₋₃ alkylsulfinyl, C₁₋₂ alkoxy, halo, or C₁₋₄ alkyl;

20

provided that:

(A) when W₃ is -(CR₄R₅)-(CR₆R₇)- or -(NR₄)-(CR₆R₇)- and n is 1; R₂, R₈ and R₄, R₆ together represent two C=C bonds to form an aromatic pyridine ring or an aromatic pyrimidine ring; R₃, R₅, R₇ and R₉ are H or one or more of R₃, R₅, R₇ and R₉ are independently selected from H or C₁₋₂ alkyl; or

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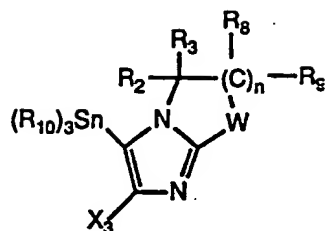
(B) when W₃ is S(O)_m or O, m is 0 and n is 1; R₃ and R₉ are H or one or more of R₃ and R₉ are independently selected from H or C₁₋₂ alkyl; R₂, R₈ forms a C=C bond in an aromatic thiazole or oxazole ring; or

30

(C) when W₃ is S(O)_m, m is 0, and n is 1 or 2; R₂, R₃, R₈ and R₉ are H or one or more of R₂, R₃, R₈ and R₉ are independently selected from H or C₁₋₂ alkyl.

The term "Formula (If)" refers a compound represented by the structure:

-52--

Formula (If)

wherein

5

W is $-\text{CR}_5=\text{CR}_7-$, $-\text{N}=\text{CR}_7-$, $-\text{S}-$ or $-\text{O}-$;

X₃ is (a) monosubstituted phenyl wherein said substituent is selected from C₁₋₃ alkylthio, C₁₋₂ alkoxy, halo, $-\text{H}$, or C₁₋₄ alkyl; or

10

(b) disubstituted phenyl wherein said substituents are independently selected from C₁₋₃ alkylthio, C₁₋₂ alkoxy, halo, C₁₋₄ alkyl, or the disubstituents together form a methylene dioxy group;

provided that:

(1.) when W is $-\text{CR}_5=\text{CR}_7-$ or $-\text{N}=\text{CR}_7-$ then

n is 1;

R₃, R₅, R₇ and R₉ are, independently, $-\text{H}$ or C₁₋₂ alkyl;

15

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is $-\text{S}-$ or $-\text{O}-$ then

n is 1;

R₃ and R₉ are, independently, $-\text{H}$ or C₁₋₂ alkyl; and

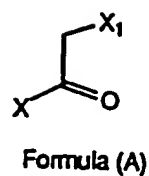
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R₂ and R₈ are, independently, $-\text{H}$ or C₁₋₂ alkyl or together represent a double bond in the B ring such that the B ring is an aromatic thiazole or oxazole ring;

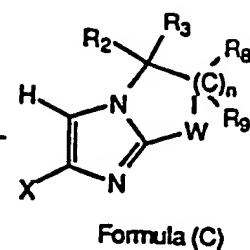
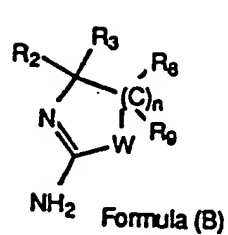
The compounds of Formula (IA) can be prepared according to the following scheme:

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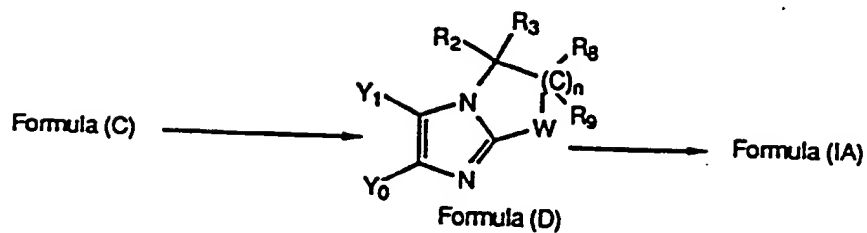
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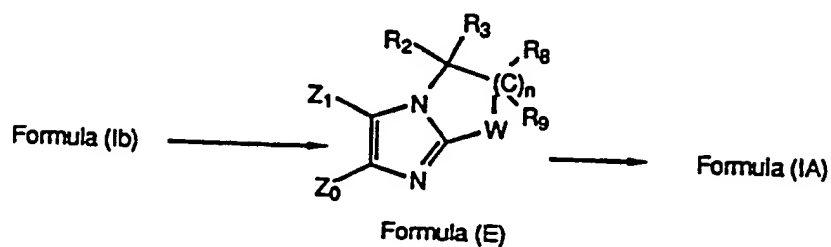


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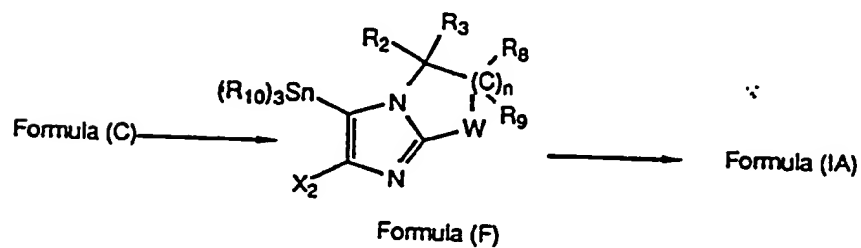


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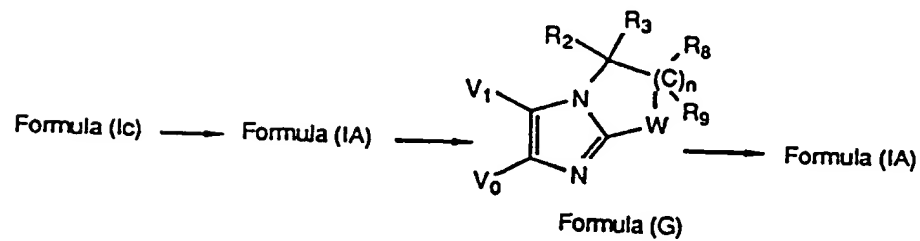


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All the necessary 1-aryl-2-halo-ethanone Formula (A) compounds wherein X_1 is a halogen such as Cl or Br and X is chosen from a group consisting of mono or disubstituted phenyl, 4-pyridyl, and alkyl-substituted 4-pyridyl, are known in the art or are prepared by treatment of the correspondingly substituted 1-phenyl-ethanones or 1-(4-pyridyl)ethanones (which are commercially available or known in the art) with one equivalent of halogen, preferably bromine, in acetic acid, 48% hydrobromic acid, or a halocarbon solvent such as chloroform. See, e.g., Langley, Org. Syn. Coll., **1**, 127 (1944) and Taurins *et al.*, J. Heterocyclic Chem., **7**, 1137 (1970). Alternatively, the mono and disubstituted 1-phenyl-2-chloro-ethanone Formula (A) compounds can be prepared by Friedel Crafts acylation of the corresponding mono or disubstituted benzenes with 2-chloroacetyl chloride and aluminum chloride by the method of Joshi *et al.*, J. Heterocyclic Chem., **16**, 1141 (1979). By these methods, Formula (A) compounds are prepared wherein X is 4-pyridyl, mono- C_{1-4} alkyl-substituted pyridyl or monosubstituted phenyl (wherein said substituent is selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, H, or C_{1-4} alkyl); or disubstituted phenyl (wherein said substituents are independently selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo or C_{1-4} alkyl; or the disubstituents together form a methylene dioxy group).

Compounds of Formula (C) as defined above are prepared from the following classes of Formula (B) compounds wherein $R_2, R_3, R_4, R_5, R_6, R_7, R_8$ or R_9 are hydrogen or are one or more C_{1-2} alkyl groups; i.e.,:

1. 2-amino-(1,3)-oxazole ($W=O$);
2. 2-amino-4,5-dihydro-(1,3)-thiazole ($W=S, n=1$);
3. 2-amino-5,6-dihydro-[4H]-(1,3)-thiazine ($W=S, n=2$);
- 2 5 4. 2-amino-(1,3)-thiazole ($W=S, n=1, R_2, R_8$ together represent a C=C bond);
5. 2-aminopyridine ($W=C(R_4R_5)-C(R_6R_7)-, n=1; R_2, R_8$ and R_4, R_6 together represent two C=C bonds); and
6. 2-aminopyrimidine ($W=(NR_4)-(CR_6R_7)-, n=1; R_2, R_8$ and R_4, R_6 together represent two C=C bonds).
- 3 0

The necessary Formula (B) compounds are commercially available or are known in the art and can be readily prepared by one of skill in the art.

The Formula (B) compound is reacted with a 1-aryl-2-halo-ethanone Formula (A) compound to afford the Formula (C) compound by alkylation followed by cyclodehydration. In this way, the following classes of Formula (C) compounds are prepared:

1. imidazo[2,1-b]oxazole ($W=O, n=1, R_2, R_8$ together represent a C=C bond);

2. 2,3-dihydroimidazo[2,1-b]thiazole ($W=S$, $n=1$);
3. 6,7-dihydro[5H]imidazo[2,1-b][1,3]thiazine ($W=S$, $n=2$);
4. imidazo[2,1-b]thiazole ($W=S$, $n=1$, R_2, R_8 together represent a C=C bond);
- 5 5. imidazo[1,2-a]pyridine ($W=C(R_4R_5)-C(R_6R_7)-$, $n=1$; R_2, R_8 and R_4, R_6 together represent two C=C bonds); and
6. imidazo[1,2-a]pyrimidine ($W=(NR_4)-(CR_6R_7)-$, $n=1$; R_2, R_8 and R_4, R_6 together represent two C=C bonds).

The reaction to form the Formula (C) compounds is performed in a nonpolar solvent such as chloroform or toluene, or in a polar nonprotic solvent such as dimethylformamide or acetonitrile. Alkylation is facilitated by the presence of one to four equivalents of a base such as powdered sodium carbonate or triethylamine, and cyclodehydration is facilitated by heating (between ambient temperature and reflux) or removing the solvent and refluxing the residue in water or dilute aqueous acid.

Compounds of Formula (D) as defined above are N-(substituted carbonyl)-1,4-dihydropyridines. The Formula (D) compounds are prepared by treatment of the corresponding Formula (C) compounds of classes 1, 4, 5 and 6 described above wherein X is selected from (a) monosubstituted phenyl (wherein said substituent is selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, H, or C_{1-4} alkyl); or (b) disubstituted phenyl (wherein said substituents are independently selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl, or the disubstituents together form a methylene dioxy group); or the corresponding Formula (C) compounds of classes 2 and 3 described above wherein X is disubstituted phenyl wherein said substituents are selected from one of the following combinations: di(C_{1-3} alkylthio); dihalo(C_{1-3} alkylthio) and C_{1-2} alkoxy; C_{1-3} alkylthio and halo; C_{1-3} alkylthio and C_{1-4} alkyl; or C_{1-2} alkoxy and halo; with a substituted carbonyl pyridinium salt by the method of Bender *et al.*, U.S. Patent 4,803,279, issued February 9, 1989, and Adams *et al.*, U.S. Patent Application Serial Number 07/255,816, filed October 11, 1988. The pyridinium salt may be either preformed or preferably prepared *in situ* by addition of the substituted carbonyl halide (such as an acyl halide, an aroyl halide, an arylalkyl haloformate ester, or preferably an alkyl haloformate ester) to a solution of the Formula (C) compound in pyridine or in an inert solvent such as methylene chloride to which pyridine has been added.

Compounds of Formula (C) may be treated with an alkyl lithium compound to yield the corresponding lithium reagent by metallation. The lithium intermediate may then be treated with an excess of magnesium halide or zinc halide etherate to yield the corresponding organometallic reagent by transmetallation. To this organometallic reagent a 4-bromo, 4-iodopyridine or the triflate ester of a 4-hydroxy

pyridine (a 4-trifluoromethylsulfonyloxypyridine) in the presence of a palladium (O) catalyst, such as tetrakis(triphenylphosphine)-palladium, with hexamethylphosphoramide; or a palladium (II) catalyst in the presence of lithium chloride and a base, such as sodium bicarbonate or triethylamine, to yield the corresponding Formula (IA) compounds. [See Kumada et al., Tetrahedron Letters, 22, 5319 (1981).]

One may also treat the lithio derivatives of Formula (C) compounds, as prepared above, with a trialkyltin halide, such as n-butyl tin chloride, to yield the intermediate compound represented herein as Formula (If). The compounds of Formula (If) may be utilized to produce the compounds of Formula (IA) wherein either R_1 or R_2 is a 4-pyridyl or mono alkylsubstituted pyridyl derivative or as a substituted phenyl. When the compounds of Formula (If) are reacted with a 4-pyridyl halide, preferably iodide, or the triflate ester of a hydroxy 4-pyridyl compound and tetrakis(triphenylphosphine)-palladium in a mixture of tetrahydrofuran and hexamethylphosphoramide or a mixture of the halide or triflate with a palladium (II) catalyst in the presence of lithium chloride and base.

The compounds of Formula (C) may also be treated with an excess of bromine to yield a 3-bromo derivative, wherein the substituent group of the phenyl on a Formula (C) compound is substituted with other than a bromine or iodine, as a halogen substituent group. To the bromo derivative of Formula (C) is added a pyridine boronic acid [$B(OH)_2$ -4-pyridyl] with a palladium catalyst such as $Pd(Ph_2P(CH_2)_4-PPh_2)Cl_2$ or $Pd(PPh_3)_4$ in the presence of about three equivalents of sodium bicarbonate for about 12 hours in reflux conditions with a DME(dimethyl ethane)/ H_2 in a 3:1 ratio. The pyridine-4-boronic acid is prepared from 4-bromopyridine by reaction with n-butyllithium, trapping of the anion with triethyl borate and acid hydrolysis of the boronate ester. The method is similar to that of Fischer and Haviniga, Rec. Trav. Chim. pays Bas, 84, 439 (1965). Additional references for coupling of bromopyridines with boronic acids are Sniechus, V., Tetrahedron Lett., 29, 2135 (1988) and Terashimia, M., Chem. Pharm. Bull., 11, 4755 (1985).

The brominated Formula (C) compound can also, following halogen-metal exchange with n-BuLi be coupled to a substituted halobenzene, preferably an iodide in the presence of bidentate palladium (II) catalyst or a $Ni(II)Cl_2$ (1,2-bis(diphenyl-phosphino)ethane) catalyst to yield the desired regioisomer of the compounds of Formula (IA). [See, Pridgen, J. Org. Chem., 47, 4319 (1982)]. The compounds of Formula (C) may be reacted in the above manner by treatment directly with a C_{1-5} alkyllithium compound to yield the corresponding lithium reagent by metallation and then proceed with the coupling reaction.

The lithio derivative of a Formula (C) compound, however derived, when X is other than a 4-mono C_{1-4} alkylpyridyl or 4-pyridyl may be coupled to a

substituted 4-halopyridine in the presence of the noted palladium (II) or Ni(II) catalyst to yield the final desired compounds of Formula (IA).

Compounds of Formula (E) as defined above serve as intermediates in the preparation of Formula (IA) compounds where one of R_0 or R_1 in the product

5 Formula (IA) compound is monoalkyl substituted pyridyl. Compounds of Formula (E) are N-(substituted carbonyl)-4-(1,2-dihydro-2-alkyl)pyridines and are prepared by the method of Comins *et al.*, *J. Org. Chem.*, **47**, 4315 (1982), i.e., by treatment of an appropriate Formula (Ib) compound in a dry ethereal solvent such as tetrahydrofuran at reduced temperature (below 0°C) with a substituted carbonyl halide (such as an acyl

10 halide, an aroyl halide, an arylalkyl haloformate ester, or preferably an alkyl haloformate ester), followed by treatment with an alkyl grignard reagent.

Formula (Ib) compounds where W_2 is $S(O)_m$, m is 0, n is 1 or 2; R_2 , R_3 , R_8 and R_9 are H or one or more of R_2 , R_3 , R_8 and R_9 are independently selected from H or C_{1-2} alkyl; one of R_1 or R_0 is selected from 4-pyridyl and the other is

15 selected from: (a) monosubstituted phenyl wherein said substituent is selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, H, or C_{1-4} alkyl; or (b) disubstituted phenyl wherein said substituents are independently selected from C_{1-2} alkoxy, C_{1-4} alkyl; or (c) the disubstituents together form a methylene dioxy group; are prepared as described in Bender *et al.*, U.S. Patent Number 4,175,127, issued November 20, 1979; Bender *et al.*, U.S. Patent Application Serial Number 07/106,199 filed on July 10, 1987; or

20 Bender *et al.*, U.S. Patent Number 4,803,279, issued February 9, 1989.

The remaining Formula (Ib) compounds, i.e., those where

(A) when W_2 is $-(CR_4R_5)-(CR_6R_7)-$ or $-(NR_4)-(CR_6R_7)-$ and n is 1;

R_2 , R_8 and R_4 , R_6 together represent two $C=C$ bonds to form an aromatic pyridine ring or an aromatic pyrimidine ring; R_3 , R_5 , R_7 and R_9 are H or one or more of R_3 , R_5 , R_7 and R_9 are independently selected from H or C_{1-2} alkyl; or

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(B) when W_2 is $S(O)_m$ or O, m is 0 and n is 1; R_3 and R_9 are H or one or more of R_3 and R_9 are independently selected from H or C_{1-2} alkyl; R_2 , R_8 forms a $C=C$ bond in an aromatic thiazole or oxazole ring; and one of R_1 or R_0 is 4-pyridyl and the other is selected from (a) monosubstituted phenyl wherein said substituent is selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, H, or C_{1-4} alkyl; or (b) disubstituted phenyl wherein said substituents are independently selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl, or the

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disubstituents together form a methylene dioxy group; or

(C) when W_2 is $S(O)_m$, m is 0, and n is 1 or 2; R_2 , R_3 , R_8 and R_9 are H or one or more of R_2 , R_3 , R_8 and R_9 are independently selected from H or C_{1-2} alkyl; and one of R_1 or R_0 is 4-pyridyl and the other is selected from

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disubstituted phenyl (wherein said substituents are selected from one of the following combinations: di(C₁₋₃ alkylthio), dihalo, (C₁₋₃ alkylthio) and C₁₋₂ alkoxy, C₁₋₃ alkylthio and halo, C₁₋₃ alkylthio and C₁₋₄ alkyl, or C₁₋₂ alkoxy and halo),

- 5 are all embraced by the scope of Formula (IA) compounds and are obtained from intermediates of Formula (D) and Formula (F) compounds as more elaborately described herein.

Compounds of Formula (D) and Formula (E) are converted into compounds of Formula (IA) by deacylation and oxidation with a mild oxidizing agent
10 by the methods described in Bender et al., U.S. Patent No. 4,803,279 and Adams et al., U.S. Patent Application Serial Number 07/255,816, filed October 11, 1988. Exemplary oxidation systems are sulfur in a refluxing inert solvent, or solvent mixture (such as decalin, decalin and diglyme, p-cymene, mesitylene), or oxygen in the presence of potassium tert.-butoxide/tert.-butanol.

- 15 Compounds of Formula (F) as defined above are intermediates to the corresponding Formula (IA) compounds and are prepared by metallation of the appropriate Formula (C) compounds, where X is 4-pyridyl or monoalkyl-substituted 4-pyridyl, with a lithiating agent (such as s-butyllithium or n-butyllithium) in an ethereal solvent (such as tetrahydrofuran), followed by treatment with a trialkyltin halide.
- 20 These Formula (F) compounds are employed to prepare the Formula (IA) compounds where R₀ is 4-pyridyl or monoalkyl-substituted 4-pyridyl, i.e., one mole equivalent of the Formula (F) compound is added to an excess of a solution of a mono- or di-substituted phenyl bromide, triflate, or preferably the iodide, in an inert solvent (such as tetrahydrofuran) preferably containing 10% hexamethylphosphoramide and 1 to 10
- 25 mole percent of a palladium (0) catalyst (such as tetrakis(triphenylphosphine)-palladium) by the method described in Adams et al., U.S. Patent Application Serial Number 07/255,816, filed October 11, 1988, or by using a palladium (II) catalyst in the presence of lithium chloride and an added base such as triethylamine. Triflate precursors are prepared from the corresponding substituted phenols by treatment with
- 30 trifluorosulfonic anhydride in the presence of a base such as pyridine or triethylamine. Formula (F) compounds where W is S(O)_m, m is 0, n is 1 or 2, and X₂ is 4-pyridyl, are treated with a disubstituted phenyl bromide, triflate or preferably the iodide, wherein the substituents are selected from one of the following combinations: di(C₁₋₃ alkylthio), dihalo, C₁₋₃ alkylthio and C₁₋₂ alkoxy, C₁₋₃ alkylthio and halo, C₁₋₃ alkylthio and C₁₋₄ alkyl, or C₁₋₂ alkoxy and halo. The remaining Formula (F)
- 35 compounds are treated with (a) a monosubstituted phenyl bromide, triflate or preferably the iodide wherein said substituent is selected from C₁₋₃ alkylthio, C₁₋₂ alkoxy, halo, H, or C₁₋₄ alkyl; or (b) a disubstituted phenyl bromide, triflate or preferably the iodide

wherein said substituents are independently selected from C₁₋₃ alkylthio, C₁₋₂ alkoxy, halo, C₁₋₄ alkyl, or the disubstituents together form a methylene dioxy group.

Refluxing this mixture for 8 to 48 hours gives the desired Formula (IA) compounds after treatment with aqueous sodium fluoride solution.

- 5 The compounds of Formula (IA) wherein R₁ is a 4-pyridyl or C₁₋₄ alkyl-4-pyridyl may also be produced through use of a tin containing intermediate referred to herein as a Formula (If) compound. The same reaction conditions and methods apply for use of a Formula (If) compound as with a Formula (F) compound. A mixture of a 4-pyridyl halide, preferably iodide, or triflate ester of a hydroxy 4-
10 pyridyl compound and tetrakis (triphenylphosphine)-palladium in a mixture of tetrahydrofuran and hexamethylphosphoramide, or a palladium (II) catalyst in the presence of lithium chloride and a base, followed by optional hydrolysis, oxidation, or reduction to yield the desired compound of Formula (IA).

- Compounds of Formula (IA) where one of R₁ or R₀ is mono or
15 disubstituted phenyl possessing one or more 1-acyloxyalkylthio substituent(s) and compounds of Formula (G) (defined above) are prepared via Pummerer
Rearrangement on the corresponding compounds of Formula (Ic). Pummerer
Rearrangement of the corresponding Formula (Ic) compounds is accomplished by the method described in Adams *et al.*, U.S. Patent Application Serial Number 07/255,816,
20 filed October 11, 1988 by refluxing with an alkanoic acid anhydride.

- The Formula (Ic) compounds wherein W₃ is S(O)_m, m is 0, n is 1 or 2; R₂, R₃, R₈ and R₉ are independently selected from H or C₁₋₂ alkyl; one of R₁ or R₀ is 4-pyridyl or mono-C₁₋₄alkyl- substituted-4-pyridyl, and the other of R₁ or R₀ is monosubstituted phenyl where said substituent is C₁₋₃ alkylsulfinyl are prepared by the
25 method described in Bender *et al.*, U.S. Patent Number 4,175,127, issued November 20, 1979, Bender *et al.*, U.S. Patent Application Serial Number 07/106,199 filed on July 10, 1987 or Bender *et al.*, U.S. Patent Number 4,803,279, issued February 9, 1989.

- The remaining Formula (Ic) compounds, i.e., those compounds of
30 Formula (Ic) wherein (A) when W₃ is -(CR₄R₅)-(CR₆R₇)- or -(NR₄)-(CR₆R₇)- and n is 1; R₂, R₈ and R₄, R₆ together represent two C=C bonds to form an aromatic pyridine ring or an aromatic pyrimidine ring; R₃, R₅, R₇ and R₉ are H or one or more of R₃, R₅, R₇ and R₉ are independently selected from H or C₁₋₂ alkyl; or (B) when W₃ is S(O)_m or O, m is 0 and n is 1; R₃ and R₉ are H or one or more of R₃ and R₉
35 are independently selected from H or C₁₋₂ alkyl; R₂, R₈ forms a C=C bond in an aromatic thiazole or oxazole ring; and one of R₁ or R₀ is 4-pyridyl or mono-C₁₋₄alkyl-substituted-4-pyridyl; and the other is selected from: (a) monosubstituted phenyl wherein said substituent is C₁₋₃ alkylsulfinyl; or (b) disubstituted phenyl wherein one

- of said substituents must be C₁₋₃ alkylsulfinyl and the other is selected from C₁₋₃ alkylsulfinyl, C₁₋₂ alkoxy, halo, or C₁₋₄ alkyl; or (c) when W₃ is S(O)_m, m is 0, and n is 1 or 2; R₂, R₃, R₈ and R₉ are H or one or more of R₂, R₃, R₈ and R₉ are independently selected from H or C₁₋₂ alkyl; and one of R₁ or R₀ is 4-pyridyl or mono-C₁₋₄alkyl-substituted-4-pyridyl; the other is selected from disubstituted phenyl wherein one of said substituents must be C₁₋₃ alkylsulfinyl and the other is selected from C₁₋₃ alkylsulfinyl, C₁₋₂ alkoxy, halo, or C₁₋₄ alkyl; are all embraced by the scope of Formula (IA) and are prepared as described herein.

- The Formula (G) compounds where one of V₁ or V₀ is mono or disubstituted phenyl having at least one mercapto substituent are obtained by hydrolysis of the Formula (IA) acyloxyalkylthio products or preferably by treatment of a Formula (Ic) compound with trifluoroacetic anhydride followed by basic solvolysis with a base such as sodium methoxide in methanol, similar to the method of R. N. Young *et al.*, Tetrahedron Letters, 25, 1753 (1984).

- Formula (G) compounds serve as intermediates for the synthesis of Formula (IA) compounds where one of R₁ or R₀ of the Formula (IA) compound is mono or disubstituted phenyl having at least one 2-alkenyl-1-thio function. A solution of the Formula (G) intermediate in a polar solvent such as dimethylformamide is treated with a strong base, such as a metal hydride, (preferably sodium hydride), a metal alkoxide or lithium diethylamide. The metal mercaptide salt is treated with a 1-halo-2-alkene such as allyl bromide and heated from 25 to 80°C to give the Formula (IA) compounds where one of R₁ or R₀ is mono or disubstituted phenyl having at least one 2-alkenyl-1-thio substituent.

- The Formula (G) compounds described above also serve as intermediates for the synthesis of Formula (IA) compounds in which one of R₁ or R₀ is mono or disubstituted phenyl having at least one 1-alkenyl-1-thio function. Treatment of the Formula (G) compound in a nonprotic solvent such as tetrahydrofuran with a strong base such as lithium diethylamide at low temperature (-78 to -20°C) generates the lithium mercaptide salt. This salt is alkylated at 0°C with a trimethylsilylmethylating agent (such as trimethylsilylmethyl halide, triflate, or acetate) to form the trimethylsilylmethylthio substituent. The latter is deprotonated with addition of another molar equivalent of lithium diethylamide and treated with an aldehyde or ketone to give the Formula (IA) compound where V₀ or V₁ is mono or disubstituted phenyl having one at least one 1-alkenyl-1-thio substituent.

- Compounds of Formula (I) or (II) wherein R or R¹ is phenyl substituted with a substituted disulfide group are prepared by mild air oxidation of the compounds of Formula (I) wherein R or R¹ is phenyl substituted with a sulphydryl group, prepared as described above. The nonsymmetrical disulfide (Z) wherein Z is -

S-S-Z₁ and Z₁ is phenyl or C₁₋₉ alkyl, the compound may be prepared by reaction of the sulfhydryl compound with the appropriate sulfenyl halide in an ethereal solvent to afford compounds of Formula (I) or (II) wherein one of R or R¹ is phenyl substituted with one or more alkyl-dithio or aryl-dithio groups. The method of Mukaiyam *et al.*, Tetrahedron Letters, 56:5907-08 (1968) allows for use of the desired aryl-SH or alkyl-SH reagent treated with diethylazodicarboxylate in 1:1 equivalence at room temperature in a solvent, yielding an adduct which is then treated with 1:1 ratio of the desired mercaptan of Formula (G). This process will also yield the disulfide dimer of the compounds of Formula (I) or (II).

1 0 Compounds of Formula (IA) where one of R₁ or R₀ is mono or disubstituted phenyl possessing a 4-halogen substituent (preferably fluoride) can be converted to the 4-alkylthio Formula (IA) compound by displacement of the halide ion with a metal alkyl-mercaptide salt (such as sodium thioethoxide) in a polar nonprotic solvent (such as dimethylformamide) heated to between 70 and 150°C. In compounds
1 5 of Formula (IA) where W is S(O)_m and the substituents R₂, R₃, R₈, R₉ are H or C₁₋₂ alkyl, m is preferably 0 for this conversion.

The Formula (G) compounds may be obtained by treatment of a halophenyl, preferably a fluoro or bromophenyl derivative of a Formula (IA) or (Ib) compound having at least one halo substituent on the phenyl ring, in dimethyl sulfoxide
2 0 (DMSO) with NaSH(sodium bisulfide) under similar conditions as formation of the Formula (IA) compounds as described above, with a metal mercaptide salt only for a longer temperature and time. A possible reaction to yield a Formula (C) or (IA) compound is to treat a halophenyl derivative of Formula (IA), (IB) or (C) with the sodium salt of an alkylmercaptan with catalytic amount of a palladium (O) compound,
2 5 such as tetrakis(triphenylphosphine)-palladium in a solvent, such as DMS. In the instance wherein the resulting Formula (IA) compound contains an alkylthiophenyl substituent, said compound may be oxidized in accordance with procedures well known to those skilled in the art, and as illustrated below for the Formula (IC) compounds, may then be used as an intermediate to make the mercapto compound of
3 0 Formula (G).

Compounds of Formula (IA) or (IC) possessing an alkylsulfinyl, 1-alkenyl-1-sulfinyl, or 2-alkenyl-1-sulfinyl mono or disubstituted phenyl ring, or those compounds of Formula (IA) where W is S(O), are prepared by oxidation of the corresponding compounds of Formula (IA) or (IC) (possessing, respectively, an
3 5 alkylthio, 1-alkenyl-1-thio or 2-alkenyl-1-thio mono or disubstituted phenyl ring or those compounds of Formula (IA) where W is S(O)_m and m is 0), by employing one equivalent of oxidizing agent per sulfide in the molecule. The oxidizing agent may be an organic peracid (such as 3-chloroperoxybenzoic) added dropwise to a solution of the

- Formula (IA) or (IB) compound in a halocarbon (such as methylene chloride) at ice bath temperature, or an inorganic agent (such as sodium periodate or hydrogen peroxide) in water added dropwise to a solution of the Formula (IA) or (IC) compound in water containing 2 equivalents of an inorganic acid (such as hydrochloric acid) at ice bath temperature. Treatment of compounds of Formula (IA) containing two sulfide functions with one equivalent of oxidant results in the formation of a mixture of the sulfoxides.

- Compounds of Formula (IA) where W is S(O)₂ are prepared by oxidation of the corresponding compounds of Formula (IA) where W is S(O) and is the only sulfoxide function in the molecule. The oxidation is achieved according to the method of Chatterway et al., *J. Chem. Soc.*, 1352 (1930), by dropwise addition of an aqueous solution of 2/3 equivalent of potassium permanganate per sulfoxide substituent to a solution of the Formula (IA) compound in water containing two equivalents of an inorganic acid such as hydrochloric acid. This oxidation is selective for sulfoxides and allows the preparation of compounds of Formula (IA) where R or R₁ is mono or disubstituted alkylthiophenyl and W is SO₂.

EXAMPLE 1

6-(4-Fluorophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo-[2,1-b]thiazole.

Formula (IA) Compound

- a) 5-(4-(1-acetyl-2-methyl)-1,2-dihydropyridyl)-6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-b]thiazole

(Formula (E) Compound.

- A stirred solution of 3.54 g (11.9 mmol) of 6-(4-fluorophenyl)-5-(4-pyridyl)-2,3-dihydroimidazo[2,1-b]-thiazole, prepared as disclosed in Bender et al., U.S. Patent Number 4,803,279, in dry tetrahydrofuran (THF) cooled between 0 and -50°C is treated sequentially with 1.84 g (23.8 mmol) of acetyl chloride and subsequently with 8.81 mL (23.8 mmol) of 2.7 M methyl magnesium bromide. The reaction mixture is allowed to come to 25°C, quenched with saturated NH₄Cl, adjusted to pH 7.5 with 10% sodium bicarbonate and extracted with methylene chloride. The combined organic extract is dried, concentrated *in vacuo* and flash chromatographed on silica to afford the title Formula (E) compound in a semi-stable form.

- b) 6-(4-Fluorophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole.

Formula (IA) Compound

- Method A

The 1-acetyl-1,2-dihydropyridine derivative of part a, above is aromatized by heating between 165 and 195°C with 1.0 g (31 mmol) of sublimed sulfur in a solution of 10% diglyme in decalin until thin layer chromatography (e.g., alumina,

methylene chloride) shows the starting material is consumed. The reaction mixture is filtered warm, and extracted into dilute aqueous HCl.

The aqueous acid phase is neutralized with 5% aqueous sodium carbonate and extracted into methylene chloride. This extract is dried, concentrated in vacuo and purified by
5 flash chromatography on silica to afford the title Formula (IA) compound.

Method B

The 1-acetyl-1,2-dihydropyridine derivative of part a, above is aromatized by adding to a stirred solution of 2.7 to 8.0 g (24-71 mmoles) of potassium t-butoxide dissolved in sieve dried t-butanol into which oxygen is being bubbled. The
1 0 solution is heated to reflux until thin layer chromatography (alumina, methylene chloride) shows the starting material is consumed. The solvent is removed in vacuo, and the residue is partitioned between 5% aqueous sodium carbonate and methylene chloride. The organic phase is washed with water and extracted into dilute aqueous HCl. The acidic aqueous phase is made alkaline with aqueous sodium carbonate and
1 5 extracted into methylene chloride. The organic layer is dried over anhydrous sodium carbonate, stripped in vacuo and the residue chromatographed on silica to afford the title Formula (IA) compound.

EXAMPLE 2

6-(4-Methylthiophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole.
2 0 Formula (IA) Compound

Method A

A stirred solution of 6.13 g (19.7 mmoles) of 6-(4-fluorophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydro-imidazo[2,1-b]thiazole, prepared as described in
2 5 Example 1b, in dry dimethylformamide (DMF) is treated with 1.65 g (23.6 mmoles) of sodium thiomethoxide under argon atmosphere and the reaction mixture heated between 75 and 140°C until the starting material has been consumed. The mixture is then cooled, poured into cold water and extracted with ethyl acetate. The organic phase is washed three times with water, dried over anhydrous sodium sulfate and stripped in vacuo. The residue is chromatographed on silica to afford the title Formula (IA)
3 0 compound.

Method B

The title compound is prepared by treatment of 6-(4-methylthiophenyl)-5-(4-pyridyl)-2,3-dihydro-imidazo[2,1-b]thiazole, prepared as disclosed in Bender et al., U.S. Patent Number 4,803,279, by the methods of Example 1a and 1b.
3 5

EXAMPLE 3

6-(4-Fluorophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo-
[2,1-b]thiazole-1-oxide.
Formula (IA) Compound

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A stirred solution of 5.08 g (16.3 mmoles) of 6-(4-fluorophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole, prepared as described in Example 1b, dissolved in chloroform is chilled in an ice bath and treated dropwise with a solution of 3.30 g (16.3 mmoles) of 85% 3-chloroperbenzoic acid in chloroform.

- 5 The solution is stirred at 25°C overnight and then is washed with 5% aqueous sodium carbonate, dried over anhydrous potassium carbonate, and stripped in vacuo. The residue is chromatographed on silica and recrystallized to give the title compound.

EXAMPLE 4

6-(4-Methylthiophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo-
[2,1-b]thiazole-1-oxide.

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Formula (IA) Compound (Method A)

The title compound is prepared by treatment of 6-(4-fluorophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole-1-oxide, prepared as described in Example 3, according to the procedure of Example 2.

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Method B

The title compound is also prepared as described in Example 6 below.

EXAMPLE 5

6-(4-Methylthiophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole-
1,1-dioxide.

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Formula (IA) Compound

A stirred mixture of 3.41 g (9.6 mmoles) of 6-(4-methylthiophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole-1-oxide, prepared as described in Example 4, in water containing 1.95 g of concentrated hydrochloric acid is treated dropwise with a solution of 1.01 g (6.38 mmoles) of potassium permanganate dissolved in water. The reaction mixture is neutralized with 5% aqueous sodium hydroxide solution. The crude product is extracted into methylene chloride, washed with water, dried over anhydrous sodium sulfate and stripped in vacuo. The residue is chromatographed on silica to give the title compound.

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EXAMPLE 6

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6-(4-Methylsulfinylphenyl)-5-(4-(2-methyl)pyridyl)-
2,3-dihydroimidazo[2,1-b]thiazole.

Formula (IA) compound

A mixture of 0.38 g (1.12 mmoles) of 6-(4-methylthiophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole, prepared as described in Example 2, in water containing 0.75 ml of 3 N hydrochloric acid is treated dropwise at 5°C with a solution of 0.241 g (1.12 mmoles) of sodium periodate in water. The reaction mixture is kept at this temperature overnight and then is warmed to 20°C and washed with methylene chloride. The aqueous phase is brought to pH 10 with sodium

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carbonate, and the crude product is extracted into methylene chloride. The organic phase is dried over anhydrous potassium carbonate, and stripped in vacuo to give a product mixture. This residue is flash chromatographed on silica and the two sulfoxides isolated to give both the title compound as well as 6-(4-methylthiophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole-1-oxide Formula (IA) compound of Example 4.

EXAMPLE 7

6-(4-Methylsulfinylphenyl)-5-(4-(2-methyl)pyridyl)-
2,3-dihydroimidazo[2,1-b]thiazole-1,1-dioxide.

10 Formula (IA) Compound

The title compound is prepared by submitting 6-(4-methylthiophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole-1,1-dioxide, prepared as described in Example 5, to the procedure of Example 6.

EXAMPLE 8

15 6-(4-Mercaptophenyl)-5-(4-(2-methyl)pyridyl)-
2,3-dihydroimidazo[2,1-b]thiazole
(Formula (G) Compound).

A solution of 5.51 g (15.5 mmoles) of 6-(4-methylsulfinylphenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole, prepared as described in Example 6, in methylene chloride cooled to 0°C is treated with 9.7 g (46.4 mmoles, 6.5 ml) of trifluoroacetic anhydride in methylene chloride. The mixture is heated to reflux for 1 hour and stripped in vacuo. The residue is treated with water and extracted into methylene chloride. The organic phase is washed with aqueous sodium bicarbonate, saturated brine, dried over anhydrous sodium sulfate and stripped in vacuo. A solution of this residue in anhydrous methanol is treated with 5 ml (23 mmoles) of a 25% solution of sodium methoxide in methanol and stirred at room temperature for 3 hours. This solution is then poured into ice-water, treated with 3N sodium bicarbonate solution, and concentrated in vacuo to remove most of the methanol. This mixture is then extracted into methylene chloride, and the organic phase is washed with water, saturated brine, dried over anhydrous sodium sulfate and stripped in vacuo. The residue is chromatographed on silica to afford the title compound.

EXAMPLE 9

6-(4-(2-Methyl-1-propenylthio)phenyl)-5-
(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole.

35 Formula (IA) Compound

A solution of 5.53 g (17 mmoles) of 6-(4-mercaptophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole, prepared as described in Example 8, in dry tetrahydrofuran at -20°C under an argon atmosphere is treated with a solution

of 17 mmoles of lithium diethylamide from 6.8 ml of 2.5 M n-butyl lithium. After warming, a solution of 1.57 g (17 mmoles) of trimethylsilylmethyl chloride in dry tetrahydrofuran is added dropwise. When the reaction is complete, the mixture is immersed in an ice-bath and a second 17 mmole solution of lithium diethylamide is added. After stirring for 15 minutes, a solution of 0.99 g (17 mmoles) of dry acetone in tetrahydrofuran is added and the reaction allowed to come to room temperature. The mixture is poured into water, extracted with methylene chloride and the organic phase dried over sodium sulfate and stripped *in vacuo*. The residue is chromatographed on silica to afford the title compound.

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EXAMPLE 10

2-(4-Methoxyphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine.Formula (IA) Compounda) 2-(4-Methoxyphenyl)imidazo[1,2-a]pyridine(Formula (C) Compound).

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A chloroform solution of 7.3 g (32 mmoles) of 1-(4-methoxyphenyl)-2-bromo-ethan-1-one and 3.0 g (32 mmoles) of 2-aminopyridine was stirred for 5 hours and a precipitate was obtained on chilling. This precipitate was washed with cold carbon tetrachloride and recrystallized from ethyl acetate to afford the title compound, melting point (mp) 135-137°C, Calcd for C₁₄H₁₂N₂O; C: 74.98; H: 5.39, N: 12.49,

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Found, C: 74.64, H: 5.35, N: 12.63.

b) 2-(4-Methoxyphenyl)-3-(1-ethoxycarbonyl-1,4-dihydropyridyl)imidazo[1,2-a]pyridine(Formula (D) Compound).

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A solution of 1.5 g (6.69 mmoles) of 2-(4-methoxyphenyl)imidazo[1,2-a]pyridine, prepared as described in Example 10a, dissolved in 20 ml of dry methylene chloride containing 5.29 g (66.9 mmoles) of pyridine was treated with 3.63 g (33.4 mmoles) of ethyl chloroformate over one hour. After 72 hours, the mixture was poured into 0.3 N HCl at 0°C and extracted into methylene chloride. The organic phase was washed with 0.3 N HCl, water and then dried over anhydrous sodium sulfate.

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The solvent was stripped *in vacuo* to give the title compound as a tan powder, ¹H-NMR (250 MHz, CDCl₃) δ 8.17 (d, 1 H), 7.60 (d, 1 H), 7.50 (d, 2 H), 7.12 (d-d, 1 H), 7.0 (br s, 2 H), 6.92 (d, 2 H), 6.76 (t, 1 H), 5.02 (p, 1 H), 4.79 (br s, 2 H), 4.32 (q, 2 H), 3.76 (s, 3 H), 1.30 (t, 3 H).

c) 2-(4-Methoxyphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine

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Formula (IA) Compound.

A mixture of 1.2 g (3.20 mmoles) of 2-(4-methoxy-phenyl)-3-(1-ethoxycarbonyl-1,4-dihydropyridyl)-imidazo[1,2-a]pyridine, prepared as described in

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Example 10b, in 10 ml of decalin was heated at 185 to 190°C under argon with 0.154 g (4.8 mmoles) of sublimed sulfur for 1.5 hours. The cooled reaction mixture was extracted with 3N HCl and the aqueous layer washed with methylene chloride, made alkaline with 5% sodium carbonate solution and extracted with methylene chloride.

- 5 The basic organic phase was dried over anhydrous potassium carbonate and stripped in vacuo. The residue was chromatographed on silica and eluted with 1 to 8% of methanol in chloroform/ethyl acetate (1:1). Recrystallization two times from ethyl acetate/ether and once from ethyl acetate/hexane gave the title compound, mp 127.5-128.5°C, Calcd for C₁₉H₁₅N₃O; C: 75.73, H: 5.02, N: 13.94; found C: 75.96, H: 5.05, N: 14.00.

EXAMPLE 11

2-(4-Fluorophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine.

Formula (IA) Compound

a) 2-(4-Fluorophenyl)imidazo[1,2-a]pyridine

1 5 (Formula (C) Compound).

1-(4-Fluorophenyl)-2-bromo-1-ethanone is reacted by the method of Example 10a, and such reaction is followed by evaporation of the solvent and reflux of the crude product in water or dilute aqueous HCl. The mixture is treated with 5% aqueous sodium carbonate and extracted with methylene chloride. The organic phase is dried and evaporated to give the title compound.

b) 2-(4-Fluorophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine.

Formula (IA) Compound

- 2 0 The title compound is prepared by treating 2-(4-fluorophenyl)imidazo[1,2-a]pyridine, prepared as described in Example 11a, according to the method of Example 10b and 10c.

EXAMPLE 12

2-(4-Methylthiophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine

Formula (IA) Compound

- 3 0 The title compound is prepared by treating 2-(4-Fluorophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine, prepared as described in Example 11, according to the method of Example 2.

EXAMPLE 13

2-(4-Methylsulfinylphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine

Formula (IA) Compound

- 3 5 The title compound is prepared by treating 2-(4-methylthiophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine, prepared as described in Example 12, according to the method of Example 6.

EXAMPLE 14

2-(4-Acetoxyethylthiophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine.

Formula (IA) Compound

To 1 g (2.7 mmoles) of 2-(4-methylsulfinylphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine, prepared as described in Example 13, is added 25 ml of acetic anhydride, and the mixture is heated to reflux for one hour. After cooling, the mixture is stripped *in vacuo*, treated with water and extracted with methylene chloride. The organic phase is washed with 3 N sodium bicarbonate and saturated aqueous sodium chloride solution, dried over sodium sulfate and stripped *in vacuo*. The residue is chromatographed on silica to give the title compound.

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EXAMPLE 15

2-(4-Mercaptophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine

Formula (G) Compound

The title compound is prepared by treating 2-(4-methylsulfinylphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine, prepared as described in Example 13, according to the method of Example 8.

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EXAMPLE 16

2-(4-(2-propenyl-1-thio)phenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyridine.

Formula (IA) Compound

A solution of 0.5 g (1.65 mmoles) of 2-(4-mercaptophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine, prepared as described in Example 15, in dry dimethylformamide under an argon atmosphere is treated with 0.079 g (1.98 mmoles) of 60% sodium hydride and stirred at room temperature for one hour. A solution of 0.24 g (1.98 mmoles) of 2-propenyl bromide in dimethylformamide is then added dropwise and heated between 25 and 65°C until the reaction is complete. The mixture is then poured into ice water and extracted three times with ethyl acetate. The organic phase is washed three times with water, dried over anhydrous potassium carbonate and concentrated *in vacuo*. The residue is chromatographed on silica to afford the title compound.

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EXAMPLE 17

2-(4-Pyridyl)-3-(4-methylsulfinylphenyl)imidazo[1,2-a]pyridine.

30 Formula (IA) Compound

a) 2-(4-Pyridyl)imidazo[1,2-a]pyridine

(Formula (C) Compound.

A stirred suspension of 1.0 g (3.6 mmoles) of 4-(bromoacetyl)pyridine hydrobromide and 1.02 g (10.8 mmoles) of 2-aminopyridine in dry dimethylformamide is treated with 0.76 g (7.2 mmoles) of powdered anhydrous sodium carbonate and heated between 35 and 100°C under an argon atmosphere until no further product forms. The solvent is removed *in vacuo* and the residue is dissolved in water. The aqueous mixture is extracted with chloroform and the organic phase washed with

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water, dried over anhydrous potassium carbonate and stripped in vacuo. The residue is chromatographed on silica to afford the title compound.

b) 2-(4-Pyridyl)-3-(imidazo[1,2-a]pyridyl)-tri-n-butyltin
(Formula (F) Compound).

5 A cold (-20 to -5°C) solution of 0.53 g (2.7 mmoles) of 2-(4-pyridyl)imidazo[1,2-a]pyridine, prepared as described in Example 17a, in dry tetrahydrofuran under an argon atmosphere is treated dropwise with 1.08 ml (2.7 mmoles) of a 2.5 M solution of n-butyllithium in hexane over 20 minutes. The reaction mixture is stirred until all the starting material is lithiated and then a solution of 1.0 g
10 (3.07 mmoles) of tri-n-butyltin chloride in dry tetrahydrofuran is added dropwise. After stirring for one hour, the mixture is treated with a saturated aqueous solution of ammonium chloride. The organic layer is washed again with aqueous ammonium chloride and dried over anhydrous potassium carbonate. The solvent is stripped in vacuo and the residue extracted with hexane and chromatographed on silica with
15 solvent containing 1% diethylamine. Removing the solvent in vacuo affords the title compound.

c) 2-(4-Pyridyl)-3-(4-methylthiophenyl)imidazo[1,2-a]pyridine.
Formula (IA) Compound

A solution of 2.69 g (10.9 mmoles) of 1-methylthio-4-iodobenzene in
20 dry tetrahydrofuran containing 10% hexamethylphosphoramide is purged by bubbling with argon for several minutes and then treated with 240 mg of tetrakis(triphenylphosphine)palladium. The mixture was heated at 50°C for several minutes and then treated with a solution of 1.73 g (3.57 mmoles) of 2-(4-pyridyl)-3-(imidazo[1,2-a]pyridyl)-tri-n-butyltin, prepared as described in Example 17b above, in
25 dry tetrahydrofuran. The mixture is refluxed until all the tin compound is gone, then it is cooled, ethyl acetate is added, and the mixture is washed with 10% aqueous sodium fluoride solution, three times with water and extracted into cold dilute HCl. The aqueous phase is washed with methylene chloride, made alkaline with 10% sodium hydroxide, and the product extracted into methylene chloride. The organic phase is
30 dried over anhydrous potassium carbonate, stripped in vacuo and the residue chromatographed on silica to afford the title compound.

d) 2-(4-Pyridyl)-3-(4-methylsulfinylphenyl)imidazo[1,2-a]pyridine.
Formula (IA) Compound

The title compound is prepared by treating 2-(4-pyridyl)-3-(4-methylthiophenyl)imidazo[1,2-a]pyridine, prepared as described in Example 17c,
35 according to the method of Example 6.

EXAMPLE 18

6-(4-Fluorophenyl)-5-(4-pyridyl)imidazo[2,1-b]thiazole.

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Formula (IA) Compound

The title compound is prepared by treating 2-aminothiazole by the method of Example 11a and 11b.

EXAMPLE 19

5 6-(4-Methylthiophenyl)-5-(4-pyridyl)imidazo[2,1-b]thiazole.

Formula (IA) Compound

The title compound is prepared by treating 6-(4-Fluorophenyl)-5-(4-pyridyl)-imidazo[2,1-b]thiazole, prepared as described in Example 18, according to the method of Example 2.

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EXAMPLE 20

6-(4-Methylsulfinylphenyl)-5-(4-pyridyl)imidazo[2,1-b]thiazole.

Formula (IA) Compound

The title compound is prepared by treating 6-(4-methylthiophenyl)-5-(4-pyridyl)imidazo[2,1-b]thiazole, prepared as described in Example 19, according to the method of Example 6.

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EXAMPLE 21

6-(4-Fluorophenyl)-5-(4-pyridyl)imidazo[2,1-b]oxazole.

Formula (IA) Compound

The title compound is prepared by treating 2-aminooxazole according to the method of Example 11a and 11b.

20

EXAMPLE 22

6-(4-Methylthiophenyl)-5-(4-pyridyl)imidazo[2,1-b]oxazole.

Formula (IA) Compound

The title compound is prepared by treating 6-(4-Fluorophenyl)-5-(4-pyridyl)imidazo[2,1-b]oxazole, prepared as described in Example 21, according to the method of Example 2.

25

EXAMPLE 23

6-(4-Methylsulfinylphenyl)-5-(4-pyridyl)imidazo[2,1-b]oxazole.

Formula (IA) Compound

The title compound is prepared by treating 6-(4-methylthiophenyl)-5-(4-pyridyl)-imidazo[2,1-b]oxazole, prepared as described in Example 22, according to the method of Example 6.

30

EXAMPLE 24

2-(4-Fluorophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyrimidine.

35 Formula (IA) Compound

a) 2-(4-Fluorophenyl)imidazo[1,2-a]pyrimidine

Formula (C) Compound).

The title compound is prepared by treating

2-aminopyrimidine according to the method of Example 11a and 11b.

b) 2-(4-Fluorophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyrimidine.

Formula (IA) Compound

5 The title compound is prepared by treating 2-(4-fluorophenyl)-imidazo[1,2-a]pyrimidine, prepared as described in Example 24a, according to the method of Example 10b and 10c.

EXAMPLE 25

2-(4-Methylthiophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyrimidine

Formula (IA) Compound

1 0 The title compound is prepared by treating 2-(4-Fluorophenyl)-3-(4-pyridyl)-imidazo[1,2-a]pyrimidine, prepared as described in Example 24, according to the method of Example 2.

EXAMPLE 26

2-(4-Methylsulfinylphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyrimidine

1 5 Formula (IA) Compound

The title compound is prepared by treating 2-(4-methylthiophenyl)-3-(4-pyridyl)-imidazo[1,2-a]-pyrimidine, prepared as described in Example 25, according to the method of Example 6.

EXAMPLE 27

2 0 2-(4-Methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro[5H]imidazo[2,1-b][1,3]thiazine.

Formula (IA) Compound

The title compound is prepared by treating 2-(4-fluorophenyl)-3-(4-pyridyl)-6,7-dihydro[5H]imidazo-[2,1-b][1,3]thiazine, prepared as disclosed in Bender *et al.*, U.S. Patent Number 4,803,279, according to the method of Example 2.

2 5 Formula (IA) Compound

The title compound is prepared by treating 2-(4-methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro[5H]imidazo-[2,1-b][1,3]thiazine, prepared as described in Example 27 above according to the method of Example 6.

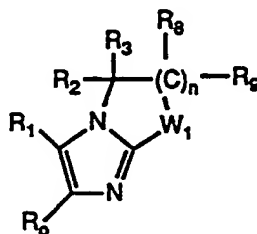
3 0 The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

3 5

CLAIMS

What is claimed is:

1. A method of inhibiting the production of interleukin-1 (IL-1) by monocytes and/or
 5 macrophages in a human in need thereof which comprises administering to such human an effective, IL-1 production inhibiting amount of a compound of the formula



FORMULA (I)

10 wherein:

W₁ is -(CR₄R₅)-(CR₆R₇)-, -CR₅=CR₇-, -N=CR₇-, -S(O)_m-
 or -O-;

n is 0 to 2;

- 15 one of R₁ and R₀ is 4-pyridyl or C₁₋₄ alkyl-4-pyridyl, provided that when R₁ is C₁₋₄ alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R₁ and R₀ is

- 20 (a) phenyl or monosubstituted phenyl wherein said substituent is C₁₋₃ alkylthio, C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-thio, C₂₋₅ 1-alkenyl-1-sulfinyl, C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-sulfinyl, 1-acyloxy-1-alkylthio, C₁₋₂ alkoxy, halo, C₁₋₄ alkyl or Z wherein Z is -S-S-Z₁ and Z₁ is phenyl or C₁₋₉ alkyl; or

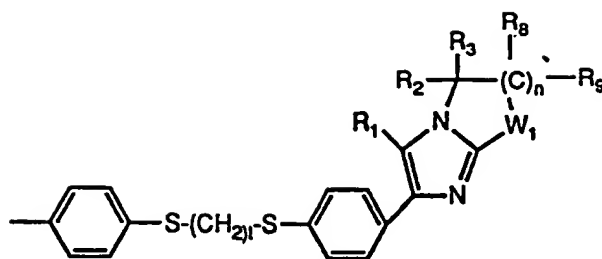
(b) disubstituted phenyl wherein said substituents are, independently, C₁₋₃ alkylthio, C₁₋₂ alkoxy, halo or C₁₋₄ alkyl; or

- 25 (c) disubstituted phenyl wherein one of said substituents is C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-thio, C₂₋₅ 1-alkenyl-1-sulfinyl, C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio and the other is C₁₋₂ alkoxy, halo, or C₁₋₄ alkyl;

- 30 (d) disubstituted phenyl wherein the substituents are the same and are C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-thio, C₂₋₅ 1-alkenyl-1-sulfinyl, C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group; or

(e) monosubstituted phenyl wherein the substituent is

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t is 0 or 1; W_1 , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are as defined above;

5 provided that:

(1.) when W_1 is $-(CR_4R_5)-(CR_6R_7)-$ then

n is 0 or 1; and

R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , and R_9 are, independently, -H or C_{1-2} alkyl; and when R_1 or R_0 is 4-pyridyl, the other of R_1 and R_0 is other than mono- C_{1-2} alkoxy-substituted phenyl or mono-halo-substituted phenyl; or

when n is 0, R_4 and R_5 together form an oxo; R_4 and R_5 may both be fluoro, or one of R_4 and R_5 is H and the other is OH; or

(2.) when W_1 is $-CR_5=CR_7-$ or $-N=CR_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are, independently, -H or C_{1-2} alkyl; and

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring;

(3.) when W_1 is $S(O)_m$ then

m is 0, 1 or 2;

n is 1 or 2; and

R_3 and R_9 are, independently, -H or C_{1-2} alkyl;

R_2 and R_8 are, independently, -H or C_{1-2} alkyl or R_2 and R_8 together represent a

double bond in the B ring such that the B ring is an aromatic thiazole ring;

further provided that:

(a) when R_2 and R_8 are, independently, -H or C_{1-2} alkyl and R_1 or R_0 is 4-pyridyl, then the other of R_1 and R_0 is other than mono- C_{1-2} alkoxy-substituted phenyl or mono-halo-substituted phenyl; and

(b) when R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring, then m is 0 and n is 1; and

(4) when W_1 is -O- then

n is 1;

R_3 and R_9 are, independently, -H or C_{1-2} alkyl; and

R_2 and R_8 together represent a double bond in the B ring such that the

5 B ring is an aromatic oxazole ring;

or a pharmaceutically acceptable salt thereof.

2. The method of Claim 1 wherein:

W_1 is $-(CR_4R_5)-(CR_6R_7)-$, $-CR_5=CR_7-$, or $-S(O)_m-$;

10 one of R_1 and R_0 is 4-pyridyl or C_{1-2} alkyl-4-pyridyl, provided that when R_1 is C_{1-2} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

(a) monosubstituted phenyl wherein said substituent is C_{1-2} alkylthio, C_{1-3} alkylsulfinyl, 1-acyloxy-1-alkylthio, C_{1-2} alkoxy or halo; or

15 (b) disubstituted phenyl wherein said substituents are, independently, C_{1-2} alkylthio or C_{1-2} alkoxy, or

(c) disubstituted phenyl wherein one of said substituents is C_{1-2} alkylsulfinyl or 1-acyloxy-1-alkylthio and the other is C_{1-2} alkoxy, or

20 (d) disubstituted phenyl wherein the substituents are the same and are C_{1-2} alkylsulfinyl or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group;

provided that:

(1.) when W_1 is $-(CR_4R_5)-(CR_6R_7)-$ then

25 n is 0 or 1; and

R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , and R_9 are -H; and

when R_1 or R_0 is 4-pyridyl, the other of R_1 and R_0 is other than mono- C_{1-2} alkoxy-substituted phenyl or mono-halo-substituted phenyl; or

30 when n is 0, R_4 and R_5 together form an oxo; R_4 and R_5 may both be fluoro, or one of R_4 and R_5 is H and the other is OH; or

(2.) when W_1 is $-CR_5=CR_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are -H; and

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic pyridine ring;

35

(3.) when W_1 is $S(O)_m$ then

m is 0, 1 or 2;

n is 1 or 2; and

-75-

R₃ and R₉ are -H;

R₂ and R₈ are -H or R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring;

further provided that:

5 (a) when R₂ and R₈ are -H and R₁ or R₀ is 4-pyridyl, then the other of R₁ and R₀ is other than mono-C₁₋₂ alkoxy-substituted phenyl or mono-halo-substituted phenyl; and

(b) when R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring, then
10 m is 0 and n is 1; and

(4) when W₁ is -O- then

n is 1;

R₃ and R₉ are -H; and

15 R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring;

or a pharmaceutically acceptable salt thereof.

3. The method of Claim 2 wherein the compound is

20 2-(4-methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;

2-(4-methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;

2-(4-ethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;

25 2-(4-ethylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;

2-(4-methylthiophenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;

30 2-(4-methylsulfinylphenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;

2-(4-methoxyphenyl)-3-(4-pyridyl)-imidazo-[1,2-a]-pyridine;

5-(3,4-(methylenedioxy)phenyl)-6-(4-pyridyl)-2,3-dihydroimidazo-2,1-b]-thiazole;

35 2-(4-methoxyphenyl)-3-(4-(2-methyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;

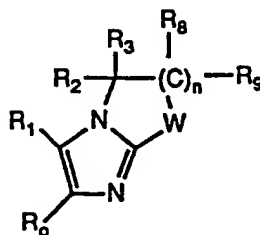
2-(4-acetoxymethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;

- 2-(trimethylacetylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
- 6-(4-methylthiophenyl)-5-(4-pyridyl)-2,3-dihydro-imidazo[2,1-b]thiazole;
- 5 5-(4-methylthiophenyl)-6-(4-pyridyl)-2,3-dihydro-imidazo[2,1-b]thiazole;
- 3-(4-methylthiophenyl)-2-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
- 10 2-(4-propylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]imidazole;
- 2-(4-methylthiophenyl)-3-(4-(2-ethyl)pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;
- 2-(4-Mercaptophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole disulfide;
- 15 2-Phenyl-3-pyridyl-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;
- 2-(4-Methoxyphenyl)-3-(4-pyridyl)-6,7-[5H]-pyrrolo-[1,2-a]imidazole;
- 6-(4-Methoxyphenyl)-5-(4-pyridyl)-2,3-dihydroimidazo[2,1-b]-thiazole;
- 2-4-Bromophenyl-3-pyridyl-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole;
- 20 2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-[7H]-pyrrolo-[1,2-a]imidazole;
- 5,6-dihydro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]-imidazole-7-ol; or
- 25 5,6-dihydro-7,7-difluoro-2-(4-Methoxyphenyl)-3-(4-pyridyl)-[7H]-pyrrolo-[1,2-a]imidazole;

or a pharmaceutically acceptable salt of any one of the above compounds.

4. The method of Claims 1 to 3 wherein the route of administration is parenteral, oral, topical, or by inhalation.
- 30

5. A compound of the formula:



FORMULA (IA)

wherein:

W is $-\text{CR}_5=\text{CR}_7-$, $-\text{N}=\text{CR}_7-$, $-\text{S}(\text{O})_m-$ or $-\text{O}-$;

5 one of R_1 and R_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that when R_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

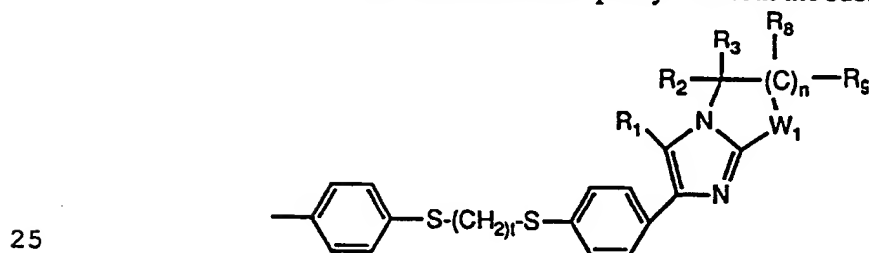
(a) phenyl or monosubstituted phenyl wherein said substituent is C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, 1-acyloxy-1-alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl or Z
10 wherein Z is $-\text{S}-\text{S}-\text{Z}_1$ and Z_1 is phenyl or C_{1-9} alkyl; or

(b) disubstituted phenyl wherein said substituents are, independently, C_{1-3} alkylthio, C_{1-2} alkoxy, halo or C_{1-4} alkyl; or

(c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio and the other is C_{1-2} alkoxy, halo, or C_{1-4} alkyl;

(d) disubstituted phenyl wherein the substituents are the same and are C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group; or

(e) monosubstituted phenyl wherein the substituent is



t is 0 or 1; W_1 , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are as defined above;

provided that:

(1.) when W is $-\text{CR}_5=\text{CR}_7-$ or $-\text{N}=\text{CR}_7-$ then

30 n is 1;

R_3 , R_5 , R_7 and R_9 are, independently, $-\text{H}$ or C_{1-2} alkyl;

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is $\text{S}(\text{O})_m$;

m is 0, 1 or 2;

n is 1 or 2;

R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; and

R₂ and R₈ are, independently, -H or C₁₋₂ alkyl; then

5 one of R₁ or R₀ is 4-pyridyl, and the other of R₁ and R₀ is:

(a) monosubstituted phenyl wherein said substituent is selected from C₂₋₅ 1-alkenyl-1-thio, C₂₋₅ 1-alkenyl-1-sulfinyl, C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-sulfinyl, 1-acyloxy-1-alkylthio; or

10 (b) disubstituted phenyl wherein said substituents are independently selected from C₁₋₃ alkylthio or halo; or

(c) disubstituted phenyl wherein one of said substituents must be C₁₋₃ alkylthio, C₁₋₃ alkylsulfinyl, C₂₋₅ 1-alkenyl-1-thio, C₂₋₅ 1-alkenyl-1-sulfinyl, C₃₋₅ 2-alkenyl-1-thio, C₃₋₅ 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio and the other is selected from C₁₋₂ alkoxy, halo or C₁₋₄ alkyl; and

(3.) when W is S(O)_m;

m is 0;

n is 1; and

20 R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; then R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; and

(4.) when W is -O- then

n is 1;

25 R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; and

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring; or

or a pharmaceutically acceptable salt thereof.

30 6. The compound of Claim 5 wherein:

W is -CR₅=CR₇-, -N=CR₇-, -S(O)_m- or -O-;

one of R₁ and R₀ is 4-pyridyl or C₁₋₂ alkyl-4-pyridyl, provided that when R₁ is C₁₋₂ alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R₁ and R₀ is

35 (a) monosubstituted phenyl wherein said substituent is C₁₋₂ alkylthio, C₁₋₂ alkylsulfinyl, C₂₋₃ 1-alkenyl-1-thio, 2-propenyl-1-thio, 1-acyloxy-1-alkylthio, C₁₋₂ alkoxy, halo; or

(b) disubstituted phenyl wherein said substituents are, independently, C₁₋₂alkylthio or C₁₋₂alkoxy; or

(c) disubstituted phenyl wherein one of said substituents is C₁₋₂alkylsulfinyl, C₂₋₃ 1-alkenyl-1-thio, 2-propenyl-1-thio or 1-acyloxy-1-alkylthio and the other is C₁₋₂alkoxy; or

(d) disubstituted phenyl wherein the substituents are the same and are C₁₋₂alkylsulfinyl, C₂₋₃ 1-alkenyl-1-thio, 2-propenyl-1-thio or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group;

10 provided that:

(1.) when W is -CR₅=CR₇- or -N=CR₇- then

n is 1;

R₃, R₅, R₇ and R₉ are -H;

15 R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is S(O)_m;

m is 0, 1 or 2;

n is 1 or 2;

R₃ and R₉ are -H; and

20 R₂ and R₈ are -H; then

one of R₁ or R₀ is 4-pyridyl, and the other of R₁ and R₀ is:

(a) monosubstituted phenyl wherein said substituent is selected from C₂₋₃ 1-alkenyl-1-thio, 2-propenyl-1-thio or 1-acyloxy-1-alkylthio; or

25 (b) disubstituted phenyl wherein said substituents are C₁₋₂alkylthio; or

(c) disubstituted phenyl wherein one of said substituents must be C₁₋₂alkylthio, C₁₋₂alkylsulfinyl, C₂₋₃ 1-alkenyl-1-thio, 2-propenyl-1-thio, or 1-acyloxy-1-alkylthio and the other is C₁₋₂alkoxy; and

30 (3.) when W is S(O)_m;

m is 0;

n is 1; and

35 R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; then

R₃ and R₉ are, -H; and

(4.) when W is -O- then

n is 1;

R₃ and R₉ are -H; and
R₂ and R₈ together represent a double bond in the B ring such that the
B ring is an aromatic oxazole ring;
or a pharmaceutically acceptable salt thereof.

5

7. The compound of Claim 6 which is

6-(4-fluorophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole;

6-(4-methylthiophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo-
[2,1-b]thiazole;

10

6-(4-fluorophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo[2,1-b]-
thiazole-1-oxide;

6-(4-methylthiophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo-
[2,1-b]thiazole-1-oxide;

15

6-(4-methylthiophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo-
[2,1-b]thiazole-1,1-dioxide;

6-(4-methylsulfinylphenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo-
[2,1-b]thiazole;

6-(4-methylsulfinylphenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo-
[2,1-b]thiazole-1,1-dioxide;

20

6-(4-(2-methyl-1-propenylthio)phenyl)-5-(4-(2-methyl)pyridyl)-2,3-
dihydroimidazo[2,1-b]thiazole;

2-(4-methoxyphenyl)-3-(4-pyridyl)imidazo[1,2-a]-pyridine;

2-(4-fluorophenyl)-3-(4-pyridyl)imidazo[1,2-a]-pyridine;

2-(4-methylthiophenyl)-3-(4-pyridyl)imidazo[1,2-a]-pyridine;

25

2-(4-methylsulfinylphenyl)-3-(4-pyridyl)imidazo[1,2-a]-pyridine;

2-(4-acetoxymethylthiophenyl)-3-(4-pyridyl)imidazo[1,2-a]-pyridine;

2-(4-(2-propenyl-1-thio)phenyl)-3-(4-pyridyl)-imidazo[1,2-a]-pyridine;

2-(4-pyridyl)-3-(4-methylsulfinylphenyl)imidazo[1,2-a]-pyridine;

2-(4-pyridyl)-3-(4-methylthiophenyl)imidazo[1,2-a]-pyridine;

30

2-(4-pyridyl)-3-(4-methylsulfinylphenyl)imidazo[1,2-a]-pyridine;

6-(4-fluorophenyl)-5-(4-pyridyl)imidazo[2,1-b]-thiazole;

6-(4-methylthiophenyl)-5-(4-pyridyl)imidazo[2,1-b]-thiazole;

6-(4-methylthiophenyl)-5-(4-pyridyl)imidazo[2,1-b]-oxazole;

6-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazo[2,1-b]-oxazole;

35

2-(4-fluorophenyl)-3-(4-pyridyl)imidazo[1,2-a]-pyrimidine;

2-(4-methylthiophenyl)-3-(4-pyridyl)imidazo[1,2-a]-pyrimidine;

2-(4-methylsulfinylphenyl)-3-(4-pyridyl)imidazo[1,2-a]pyrimidine;

2-(4-methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-imidazo-

[2,1-b][1,3]thiazine; or
 2-(4-methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro[5H]imidazo-
 [2,1-b][1,3]thiazine;
 or a pharmaceutically acceptable salt of any one of the above compounds.

5

8. The compound of Claim 7 which is 2-(4-methoxyphenyl)-3-(4-pyridyl)-imidazo-[1,2-a]-pyridine.

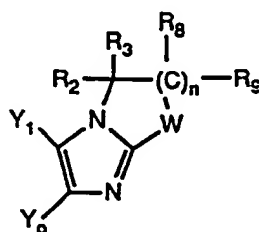
9. A pharmaceutical composition having IL-1 inhibitory activity comprising a
 10 pharmaceutically acceptable carrier or diluent and a compound of Claim 5.

10. The composition of Claim 9 wherein the compound is 2-(4-methoxyphenyl)-3-(4-pyridyl)-imidazo-[1,2-a]-pyridine.

11. The composition of Claim 9 which is in a form suitable for parenteral
 administration, oral administration, topical administration, or administration by
 inhalation.

12. A compound of the formula :

20



FORMULA (D)

, or a pharmaceutically acceptable salt thereof,

25 wherein:

W is -CR₅=CR₇-, -N=CR₇-, -S- or -O-;

Y₁ is 4-(1,4-dihydro)pyridyl substituted with N-(C₁₋₈ alkanoyl), N-(C₁₋₈ alkoxy carbonyl), N-benzoyl, N-phenoxy carbonyl, N-phenylacetyl, or N-benzyloxy carbonyl;

30

Y₀ is (a) phenyl or monosubstituted phenyl wherein said substituent is C₁₋₃ alkylthio, C₁₋₂ alkoxy, halo, -H, or C₁₋₄ alkyl; or (b) disubstituted phenyl wherein said substituents are, independently, C₁₋₃ alkylthio, C₁₋₂ alkoxy, halo, C₁₋₄ alkyl, or the disubstituents together form a methylene dioxy group;

provided that:

(1.) when W is $-CR_5=CR_7-$ or $-N=CR_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are, independently, -H

or C_{1-2} alkyl;

R_2 and R_8 together represent a double bond across the two adjacent carbon atoms in the B ring so as to form an aromatic pyridine or pyrimidine ring; and

(2.) when W is -S- or -O- then

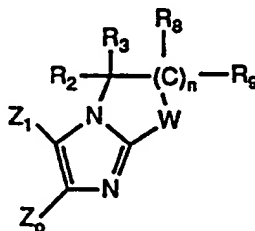
n is 1;

R_3 and R_9 are, independently, -H or C_{1-2} alkyl; and

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic thiazole or oxazole ring.

13. The compound of Claim 12 which is 2-(4-methoxyphenyl)-3-(1-ethoxycarbonyl-1,4-dihydropyridyl)-imidazo[1,2-a]pyridine or a pharmaceutically acceptable salt thereof.

14. A compound of the formula:



FORMULA (E)

, or a pharmaceutically acceptable salt thereof,

wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

one of Z_1 and Z_0 is 4-(1,2-dihydro-2-

alkyl)pyridyl substituted with N-(C1-8 alkanoyl), N-(C1-8 alkoxy carbonyl), N-benzoyl, N-phenoxy carbonyl, N-phenylacetyl, or N-benzyloxy carbonyl; and the other of Z_1 and Z_0 is

(a) phenyl or monosubstituted phenyl wherein said substituent is selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, -H, or C_{1-4} alkyl; or

(b) disubstituted phenyl wherein said substituents are independently selected from C₁₋₃ alkylthio, C₁₋₂ alkoxy, halo, C₁₋₄ alkyl, or the disubstituents together form a methylene dioxy group;

provided that:

5 (1.) when W is -CR₅=CR₇- or -N=CR₇- then

n is 1;

R₃, R₅, R₇ and R₉ are, independently, -H or C₁₋₂ alkyl;

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

10 (2.) when W is -S- or -O- then

n is 1;

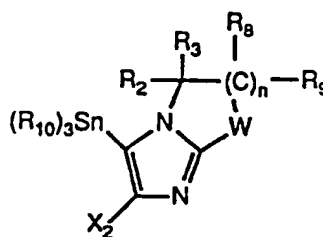
R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; and

R₂ and R₈ are, independently, -H or C₁₋₂ alkyl or together represent a double bond in the B ring such that the B ring is an aromatic thiazole or oxazole ring.

15 15. The compound of Claim 14 which is 5-(4-(1-acetyl-2-methyl)-1,2-dihydropyridyl)-6-(4-fluoro-phenyl)-2,3-dihydroimidazo[2,1-b]thiazole or a pharmaceutically acceptable salt thereof.

20

16. A compound of the formula:



FORMULA (F)

25

wherein:

W is -CR₅=CR₇-, -N=CR₇-, -S- or -O-;

R₁₀ is C₁₋₄ alkyl; and

X₂ is 4-pyridyl or mono-C₁₋₄alkyl-substituted pyridyl;

30 provided that:

(1.) when W is -CR₅=CR₇- or -N=CR₇- then

n is 1;

R₃, R₅, R₇ and R₉ are, independently, -H or C₁₋₂ alkyl;

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is -S- then

n is 1 or 2;

5 R_3 and R_9 are, independently, -H or C_{1-2} alkyl;

further provided that:

(a.) when W is -S- and n is 1 then R_2 and R_8 are, independently, -H or C_{1-2} alkyl or together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; and

10 (b.) when W is -S- and n is 2 then R_2 and R_8 are, independently, -H or C_{1-2} alkyl; and

(3.) when W is -O- then

n is 1;

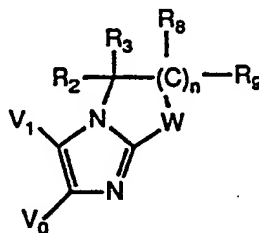
R_3 and R_9 are, independently, -H or C_{1-2} alkyl; and

15 R_2 and R_8 represent double bonds in the B ring such that the B ring is an aromatic oxazole ring.

17. The compound of Claim 16 which is 2-(4-pyridyl)-3-(imidazo[1,2-a]pyridyl)-tri-n-butyltin.

20

18. A compound of the formula:



FORMULA (G)

25

, or a pharmaceutically acceptable salt thereof,

wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

30

one of V_1 or V_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that

when V_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of V_1 and V_0 is selected from:

(a) monosubstituted phenyl wherein said substituent is mercapto;

or

(b) disubstituted phenyl wherein one of said substituents must be mercapto and the other is selected from mercapto, C₁₋₂ alkoxy, halo, or C₁₋₄ alkyl;

provided that:

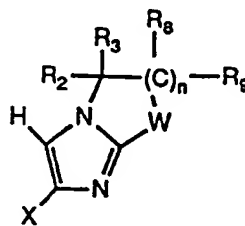
- 5 (1.) when W is -CR₅=CR₇- or -N=CR₇- then
 n is 1;
 R₃, R₅, R₇ and R₉ are, independently, -H or C₁₋₂ alkyl; and
 R₂ and R₈ together represent a double bond in
 the B ring such that the B ring is an aromatic pyridine or pyrimidine
 ring; and
- 10 (2.) when W is -S- then
 n is 1 or 2;
 R₃ and R₉ are, independently, -H or C₁₋₂ alkyl;
 further provided that:
- 15 (a) when W is -S- and n is 1 then R₂ and R₈ are, independently, -H
 or C₁₋₂ alkyl or together represent a double bond in the B ring
 such that the B ring is an aromatic thiazole ring; and
 (b) when W is -S- and n is 2 then R₂ and R₈ are, independently, -H
 or C₁₋₂ alkyl; and
- 20 (3.) when W is -O- then
 n is 1;
 R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; and
 R₂ and R₈ represent double bonds in the B ring such that the B ring is an
 aromatic oxazole ring.

25

19. The compound of Claim 18 which is
 6-(4-mercaptophenyl)-5-(4-(2-methyl)pyridyl)-2,3-dihydroimidazo-[2,1-b]-thiazole or
 2-(4-mercaptophenyl)-3-(4-pyridyl)imidazo[1,2-a]pyridine; or a pharmaceutically
 acceptable salts of any of the above compounds.

30

20. A compound of the formula:



FORMULA (C)

, or a pharmaceutically acceptable salt thereof,
wherein:

W is $-\text{CR}_5=\text{CR}_7-$, $-\text{N}=\text{CR}_7-$, $-\text{S}-$ or $-\text{O}-$;

5 X is 4-pyridyl or mono- C_{1-4} alkyl-substituted pyridyl;

provided that:

(1.) when W is $-\text{CR}_5=\text{CR}_7-$ or $-\text{N}=\text{CR}_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are, independently, $-\text{H}$ or C_{1-2} alkyl;

10 R_2 and R_8 together represent a double bond in the B ring such that the
B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is $-\text{S}-$ then

n is 1 or 2;

R_3 and R_9 are, independently, $-\text{H}$ or C_{1-2} alkyl;

15 further provided that:

(a) when W is $-\text{S}-$ and n is 1 then

R_2 and R_8 are, independently, $-\text{H}$ or C_{1-2} alkyl or together
represent a double bond in the B ring such that the B ring is an
aromatic thiazole ring; and

20 (b) when W is $-\text{S}-$ and n is 2 then

R_2 and R_8 are, independently, $-\text{H}$ or C_{1-2} alkyl; and

(3.) when W is $-\text{O}-$ then

n is 1;

R_3 and R_9 are, independently, $-\text{H}$ or C_{1-2} alkyl;

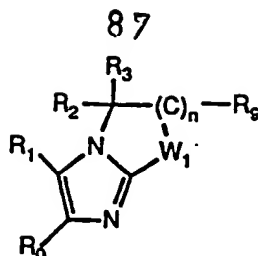
25 R_2 and R_8 together represent a double bond in the B ring such that the
B ring is an aromatic oxazole ring.

21. The compound of Claim 20 which is 2-(4-pyridyl)-imidazo-[1,2-a]-pyridine or a
pharmaceutically acceptable salt thereof.

30

22. A method of inhibiting the production of tumor necrosis factor (TNF) by
monocytes and/or macrophages in a human in need thereof which comprises
administering to such human an effective, TNF production inhibiting amount of a
compound of Formula (II):

35



wherein:

5 W_1 is $-(CR_4R_5)-(CR_6R_7)-$, $-CR_5=CR_7-$, $-N=CR_7-$, $-S(O)_m-$ or $-O-$;
one of R_1 and R_6 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that
when R_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of
the pyridine ring, and the other of R_1 and R_6 is

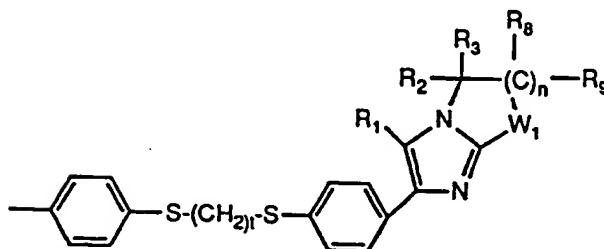
10 (a) phenyl or monosubstituted phenyl wherein said
substituent is C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio,
 C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-
sulfinyl, 1-acyloxy-1-alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl or Z
wherein Z is $-S-S-Z_1$ and Z_1 is phenyl or C_{1-9} alkyl; or

(b) disubstituted phenyl wherein said substituents are,
independently, C_{1-3} alkylthio, C_{1-2} alkoxy, halo or C_{1-4} alkyl; or

15 (c) disubstituted phenyl wherein one of said substituents is
 C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl,
 C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-1-
alkylthio and the other is C_{1-2} alkoxy, halo, or C_{1-4}
alkyl; or

20 (d) disubstituted phenyl wherein the substituents are the same
and are C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-
sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-
acyloxy-1-alkylthio or wherein the substituents together form a
methylene dioxy group;

25 (e) monosubstituted phenyl wherein the substituent is



t is 0 or 1; W_1 , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are as
defined above;

30 provided that:

(1.) when W_1 is $-(CR_4R_5)-(CR_6R_7)-$ then

n is 0;

a) and R_4 and R_5 may together form an oxo; R_4 and R_5 are both fluoro; or one of R_4 and R_5 is H and the other OH; or

5 (2.) when W_1 is $-CR_5=CR_7-$ or $-N=CR_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are, independently, -H or C_{1-2} alkyl; and

R_2 and R_8 together represent a double bond in the B ring such that the

B ring is an aromatic pyridine or pyrimidine ring;

10 (3.) when W_1 is $S(O)_m$ then

m is 0, 1 or 2;

n is 1 or 2; and

R_3 and R_9 are, independently, -H or C_{1-2} alkyl;

R_2 and R_8 are, independently, -H or C_{1-2} alkyl or R_2 and R_8

15 together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring;

further provided that:

(a) when R_2 and R_8 are, independently, -H or C_{1-2} alkyl and R_1 or R_0 is 4-pyridyl, then the other of R_1 and R_0 is
20 other a mono-fluoro-substituted phenyl; and

(b) when R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring, then m is 0 and n is 1; and

(4) when W_1 is -O- then

25 n is 1;

R_3 and R_9 are, independently, -H or C_{1-2} alkyl; and

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring;

or a pharmaceutically acceptable salt thereof.

30

23. The Method of Claim 22 wherein

W_1 is $-(CR_4R_5)-(CR_6R_7)-$, $-CR_5=CR_7-$, or $-S(O)_m-$;

one of R_1 and R_0 is 4-pyridyl or C_{1-2} alkyl-4-pyridyl,

provided that when R_1 is C_{1-2} alkyl-4-pyridyl the alkyl substituent is
35 located at the 2-position of the pyridine ring, and the other of R_1 and R_0 is

(a) monosubstituted phenyl wherein said substituent is C₁₋₂ alkylthio, C₁₋₂ alkylsulfinyl, 1-acyloxy-1-alkylthio, C₁₋₂ alkoxy or halo, or

(b) disubstituted phenyl wherein said substituents are, independently, C₁₋₂ alkylthio or C₁₋₂ alkoxy, or

(c) disubstituted phenyl wherein one of said substituents is C₁₋₂ alkylsulfinyl or 1-acyloxy-1-alkylthio and the other is C₁₋₂ alkoxy, or

(d) disubstituted phenyl wherein the substituents are the same and are C₁₋₂ alkylsulfinyl or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group;

provided that:

(1.) when W₁ is -(CR₄R₅)-(CR₆R₇)- then

n is 0;

R₄ and R₅ together may form an oxo; R₄ and R₅ are both fluoro, or one of R₄ and R₅ is H and the other OH;

(2.) when W₁ is -CR₅=CR₇- then

n is 1;

R₃, R₅, R₇ and R₉ are -H; and

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic pyridine ring;

(3.) when W₁ is S(O)_m then

m is 0, 1 or 2;

n is 1 or 2; and

R₃ and R₉ are -H;

R₂ and R₈ are -H or R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring;

further provided that:

(a) when R₂ and R₈ are -H and R₁ or R₀ is 4-pyridyl, then the other of R₁ and R₀ is other than mono-fluoro-substituted phenyl; and

(b) when R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring, then m is 0 and n is 1; and

(4.) when W is S(O)_m then

m is 0;

n is 1; and

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; then

R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; and

(5.) when W₁ is -O- then

5 n is 1;

R₃ and R₉ are -H; and

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring;

or the pharmaceutically acceptable salts thereof.

10

24. The method of Claim 22 wherein

1.) when W₁ is -(CR₄R₅)-(CR₆R₇)-;

n is 0;

15

and R₂ and R₈ are, independently, -H or C₁₋₂ alkyl and R₁ or R₀ is 4-pyridyl or C₁₋₄ alkyl-4-pyridyl then the other of R₁ and R₀ is a mono-C₁₋₃ alkylthio or C₁₋₃ alkylsulfinyl-substituted phenyl or a mono-halo-substituted phenyl;

(2.) when W₁ is S(O)_m;

20

m is 0, 1 or 2; n is 1 or 2; and R₂ and R₈ are, independently, -H or C₁₋₂ alkyl and R₁ or R₀ is 4-pyridyl, then the other of R₁ and R₀ is other than mono-fluoro-substituted phenyl.

25. The method of Claim 22 wherein the compound is

25

2-Phenyl-3-pyridyl-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;

2-4-Bromophenyl-3-pyridyl-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole;

2-(4-Pyridyl)-3-(4-fluorophenyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]

imidazole;

2-(4-Fluorophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]-

imidazole;

30

3-(4-Fluorophenyl)-2-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]-

imidazole;

2-(4-Methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]-

imidazole;

2-(4-Pyridyl)-3-(4-methylthiophenyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]-

35

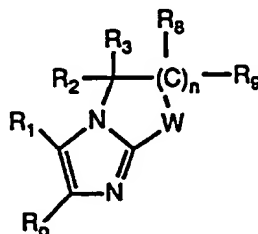
imidazole;

2-(4-Methylthiophenyl)-3-[4-(2-methylpyridyl)]-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole;

- 2-(4-Methoxyphenyl)-3-(4-pyridyl)-7-oxo-5,6-dihydro-7H-pyrrolo-[1,2-a]imidazole;
- 5,6-Dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-[7H]-pyrrolo[1,2-a]-imidazole-7-ol;
- 5 2-(4-Acetoxymethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]pyrrolo-[1,2-a]-imidazole;
- 2-(4-Methoxyphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]imidazole;
- 2-(4-Methylsulfoxyphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-
- 10 [1,2-a]imidazole;
- 2-(4-Ethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole; or
- 2-(4-Ethylsulfonylphenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
- 15
26. A method of inhibiting the production of tumor necrosis factor (TNF) by monocytes and/or macrophages in a human in need thereof which comprises administering to such human an effective, TNF production inhibiting amount of a compound known as 2-(4-methylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo[1,2-a]-imidazole; 2-(4-Ethylthiophenyl)-3-(4-pyridyl)-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole; or 2-(4-Methylthiophenyl)-3-[4-(2-methylpyridyl)]-6,7-dihydro-[5H]-pyrrolo-[1,2-a]-imidazole.
- 20
27. A method of inhibiting the production of tumor necrosis factor (TNF) by monocytes and/or macrophages in a human in need thereof which comprises administering to such human an effective, TNF production inhibiting amount of a compound known as 6-(4-Fluorophenyl)-5-(4'-pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole-1-oxide; 6-(4-Fluorophenyl)-5-(4-pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole-1,1-dioxide; or 5-(4-Fluorophenyl)-6-(4'-pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole.
- 25
28. The method of any of Claims 22 to 26 wherein the compound is administered orally, parenterally, by inhalation or topically.
- 30
29. The method of Claim 20 wherein the disease state is sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, cachexia, adult respiratory distress syndrome, bone reabsorption, cerebral malaria, chronic pulmonary
- 35

inflammatory diseases, reperfusion injury, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, Crohn's disease, ulcerative colitis, or inflammatory skin diseases, such as pyresis.

- 5 29. A process for preparing a compound of Formula (IA) represented by the structure:



10 FORMULA (IA)

or a pharmaceutically acceptable salt thereof,

wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, $-S(O)_m-$ or $-O-$;

- 15 one of R_1 and R_6 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that when R_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of R_1 and R_6 is

- 20 (a) phenyl or monosubstituted phenyl wherein said substituent is C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, 1-acyloxy-1-alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl or or Z wherein Z is $-S-S-Z_1$ and Z_1 is phenyl or C_{1-9} alkyl; or

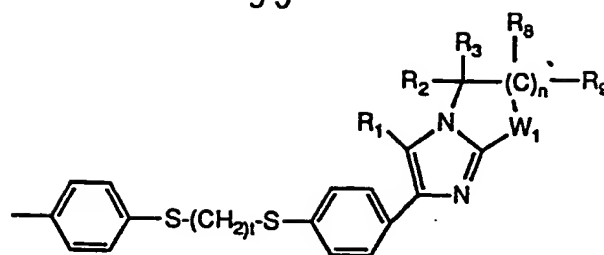
(b) disubstituted phenyl wherein said substituents are, independently, C_{1-3} alkylthio, C_{1-2} alkoxy, halo or C_{1-4} alkyl; or

- 25 (c) disubstituted phenyl wherein one of said substituents is C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio and the other is C_{1-2} alkoxy, halo, or C_{1-4} alkyl;

- 30 (d) disubstituted phenyl wherein the substituents are the same and are C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio or wherein the substituents together form a methylene dioxy group; or

(e) monosubstituted phenyl wherein the substituent is

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t is 0 or 1; W_1 , R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are as defined above;

provided that:

- 5 (1.) when W is $-CR_5=CR_7-$ or $-N=CR_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are, independently, $-H$ or C_{1-2} alkyl;

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

- 10 (2.) when W is $S(O)_m$;

m is 0, 1 or 2;

n is 1 or 2;

R_3 and R_9 are, independently, $-H$ or C_{1-2} alkyl; and

R_2 and R_8 are, independently, $-H$ or C_{1-2} alkyl; then

- 15 one of R_1 or R_0 is 4-pyridyl, and the other of R_1 and R_0 is:

(a) monosubstituted phenyl wherein said substituent is selected from C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl, 1-acyloxy-1-alkylthio; or

20 (b) disubstituted phenyl wherein said substituents are independently selected from C_{1-3} alkylthio or halo; or

(c) disubstituted phenyl wherein one of said substituents must be C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{2-5} 1-alkenyl-1-thio, C_{2-5} 1-alkenyl-1-sulfinyl, C_{3-5} 2-alkenyl-1-thio, C_{3-5} 2-alkenyl-1-sulfinyl or 1-acyloxy-1-alkylthio and the other is selected from C_{1-2} alkoxy, halo or C_{1-4} alkyl; and

- 25 (3.) when W is $S(O)_m$;

m is 0;

n is 1; and

30 R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; then

R_3 and R_9 are, independently, $-H$ or C_{1-2} alkyl; and

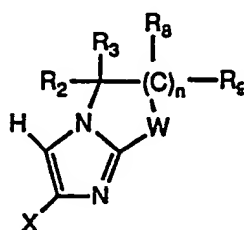
- (4.) when W is $-O-$ then

n is 1;

R_3 and R_9 are, independently, $-H$ or C_{1-2} alkyl; and

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring;

- 5 A. When it is required to prepare a compound of Formula (IA) wherein R^1 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, reacting a compound of Formula (C) represented by the structure



Formula (C)

10

wherein

n is 0 to 2;

W^1 is $-CR_5=CR_7-$, $-N=CR_7-$, $-S-$ or $-O-$;

X is a

15

a) 4-pyridyl or mono- C_{1-4} alkyl-4-pyridyl;

b) phenyl or monosubstituted phenyl wherein the substituent is selected from hydrogen, halo, C_{1-4} alkyl, C_{1-3} alkylthio, or C_{1-2} alkoxy; or

c) disubstituted phenyl wherein the substituents are selected from halo, C_{1-3} alkylthio, C_{1-3} alkyl, C_{1-2} alkoxy, or the disubstituents together form a methylene dioxy group;

20

provided that:

(1.) when W is $-CR_5=CR_7-$ or $-N=CR_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are, independently, $-H$ or C_{1-2} alkyl;

25

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is $-S-$ then

n is 1;

R_3 and R_9 are, independently, $-H$ or C_{1-2} alkyl; R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; and

30

(3.) when W is $-S-$ and

n is 1 or 2;

R_3 and R_9 are independently $-H$ or C_{1-2} alkyl;

R_2 and R_8 are independently -H or C_{1-2} alkyl; then

X is a disubstituted phenyl wherein the substituents are selected from di(C_{1-3} alkylthio), dihalo, (C_{1-3} alkylthio) and C_{1-2} alkoxy; C_{1-3} alkylthio and halo; C_{1-3} alkylthio and C_{1-4} alkyl; or C_{1-2} alkoxy and halo;

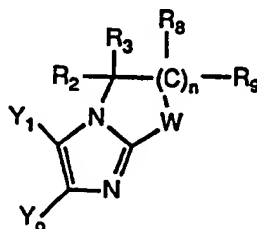
(4.) when W is -O- then

n is 1;

R_3 and R_9 are, independently, -H or C_{1-2} alkyl;

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic oxazole ring;

with pyridine in a carbonyl halide, such as an aroyl halide, or acyl halide; an arylalkyl haloformate ester, or an alkyl haloformate ester or with the preformed substituted carbonyl pyridinium salt in a solvent, such as pyridine, or a hydrocarbon solvent such as toluene, or a halohydrocarbon solvent, such as methylene chloride, provided that X is other than 4-pyridyl or mono- C_{1-4} alkyl-4-pyridyl, to yield a compound of Formula (D) as represented by the structure:



Formula (D)

or a pharmaceutically acceptable salt thereof,
wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, -S- or -O-;

Y_1 is 4-(1,4-dihydro)pyridyl substituted with N-(C_{1-8} alkanoyl), N-(C_{1-8} alkoxycarbonyl), N-benzoyl, N-phenoxy carbonyl, N-phenylacetyl, or N-benzyloxycarbonyl;

Y_0 is

(a) phenyl or monosubstituted phenyl wherein said substituent is C_{1-3} alkylthio, C_{1-2} alkoxy, halo, or C_{1-4} alkyl;

(b) disubstituted phenyl wherein said substituents are selected from halo, C_{1-3} alkylthio, C_{1-2} alkoxy, C_{1-4} alkyl, or the disubstituents together form a methylene dioxy group;

provided that:

(1.) when W is $-CR_5=CR_7-$ or $-N=CR_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are, independently, -H or C_{1-2} alkyl;

5 R_2 and R_8 together represent a double bond across the two adjacent carbon atoms in the B ring so as to form an aromatic pyridine or pyrimidine ring; and

(2.) when W is -S- or -O- then

n is 1;

10 R_3 and R_9 are, independently, -H or C_{1-2} alkyl; and

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic thiazole or oxazole ring.

(3.) when W is -S-, then

n is 1 or 2;

15 R_3 and R_9 are independently -H or C_{1-2} alkyl;

R_2 and R_8 are independently -H or C_{1-2} alkyl; and

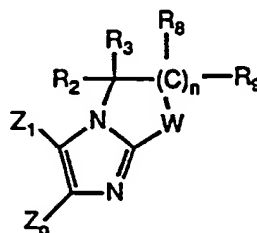
X is a disubstituted phenyl wherein the substituents are selected from di(C_{1-3} alkylthio), dihalo(C_{1-3} alkylthio) and C_{1-2} alkoxy; C_{1-3} alkylthio and halo; C_{1-3} alkylthio and C_{1-4} alkyl; or C_{1-2} alkoxy and halo;

20

followed by deacylation and oxidation of a compound of Formula (D) and optionally followed by hydrolysis, reduction, oxidation of a compound of the oxidized Formula (D) to yield the desired final compound of Formula (IA); or

25

B. When it is required to prepare a compound of Formula (IA) wherein one of R_Q or R_1 is a C_{1-4} alkyl-4-pyridyl, deacylating and aromatizing a dihydropyridine compound of Formula (E) as represented by the structure:



30

Formula (E)

or a pharmaceutically acceptable salt thereof,

wherein:

W is $-\text{CR}_5=\text{CR}_7-$, $-\text{N}=\text{CR}_7-$, $-\text{S}-$ or $-\text{O}-$;

one of Z_1 and Z_0 is 4-(1,2-dihydro-2-alkyl)pyridyl substituted with N-(C_{1-8} alkanoyl), N-(C_{1-8} alkoxycarbonyl), N-benzoyl, N-phenoxy-carbonyl, N-phenylacetyl, or N-benzyloxycarbonyl; and the other of Z_1 and Z_0 is

(a) phenyl or monosubstituted phenyl wherein said substituent is selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, $-\text{H}$, or C_{1-4} alkyl; or

(b) disubstituted phenyl wherein said substituents are independently selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl, or the disubstituents together form a methylene dioxy group;

provided that:

(1.) when W is $-\text{CR}_5=\text{CR}_7-$ or $-\text{N}=\text{CR}_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are, independently, $-\text{H}$ or C_{1-2} alkyl;

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is $-\text{S}-$ or $-\text{O}-$ then

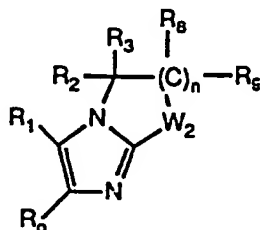
n is 1;

R_3 and R_9 are, independently, $-\text{H}$ or C_{1-2} alkyl; and

R_2 and R_8 are, independently, $-\text{H}$ or C_{1-2} alkyl or together represent a double bond in the B ring such that the B ring is an aromatic thiazole or oxazole ring;

with sulfur in a refluxing hydrocarbon solvent, such as decalin, tetralin, p-cymene, or xylene, or with potassium tert-butoxide in tert-butanol, with oxygen gas for 15 minutes, optionally followed by acylation, oxidation, reduction, hydrolysis or demethylation to yield the desired final compound of Formula (IA); or

C. When it is required to prepare a compound of Formula (E), as defined above, reacting a compound of Formula (IB) represented by the structure:



Formula (IB)

wherein:

 W_2 is $-(CR_4R_5)-(CR_6R_7)-$, $-(NR_4)-(CR_6R_7)-$, $S(O)_m$ or O;

m is 0;

5

n is 1 or 2; and

One of R_1 or R_0 is 4-pyridyl and the other is selected from:(a) phenyl or monosubstituted phenyl wherein said substituent is selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, H, or C_{1-4} alkyl;

or

10

(b) disubstituted phenyl wherein said substituents are independently selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl, or the disubstituents together form a methylene dioxy group;

provided that:

(1) when W_2 is $-(CR_4R_5)-(CR_6R_7)-$ or $-(NR_4)-(CR_6R_7)-$ and n is 1;

15

 R_2 , R_8 and R_4 , R_6 together represent two C=C bonds to form an aromatic pyridine ring or an aromatic pyrimidine ring; R_3 , R_5 , R_7 and R_9 are H or one or more of R_3 , R_5 , R_7 and R_9 are independently selected from H or C_{1-2} alkyl; or(2) when W_2 is $S(O)_m$, m is 0, and n is 1 or 2;

20

 R_2 , R_3 , R_8 and R_9 are H or one or more of R_2 , R_3 , R_8 and R_9 are independently selected from H or C_{1-2} alkyl; or(3) when W_2 is $S(O)_m$ or O, m is 0 and n is 1;

25

 R_3 and R_9 are H or one or more of R_3 and R_9 are independently selected from H or C_{1-2} alkyl; R_2 , R_8 forms a C=C bond in an aromatic thiazole or oxazole ring;

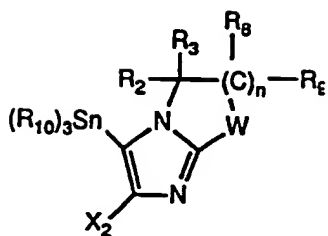
is treated in a dry ethereal solvent, such as tetrahydropyran, at reduced temperatures, with a substituted carbonyl halide, such as an acyl halide, aroyl halide; arylalkyl haloformate ester or an alkyl haloformate, followed by treatment with a C_{1-4} alkyl grignard reagent and an aqueous work up to yield the final desired compound of Formula (E) which may be further reacted to yield a compound of Formula (IA); or

30

D. When it is required to yield a compound of Formula (IA) wherein R_0 is 4-pyridyl or mono- C_{1-4} alkyl-4-pyridyl, reacting a compound of Formula (F) represented by the structure:

35

-99-

Formula (F)

wherein:

5

W is -CR₅=CR₇-, -N=CR₇-, -S- or -O-;R₁₀ is C₁₋₄ alkyl; andX₂ is 4-pyridyl or mono-C₁₋₄alkyl-substituted pyridyl;

provided that:

(1.) when W is -CR₅=CR₇- or -N=CR₇- then

10

n is 1;

R₃, R₅, R₇ and R₉ are, independently, -H or C₁₋₂ alkyl;R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is -S- then

15

n is 1 or 2;

R₃ and R₉ are, independently, -H or C₁₋₂ alkyl;

further provided that:

(a.) when W is -S- and n is 1 then R₂ and R₈ are, independently, -H or C₁₋₂ alkyl or together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; and

20

(b) when W is -S- and n is 2 then R₂ and R₈ are, independently, -H or C₁₋₂ alkyl; and

(3.) when W is -O- then

n is 1;

25

R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; andR₂ and R₈ represent double bonds in the B ring such that the B ring is an aromatic oxazole ring;

is added to

30

a) an excess of a solution of mono- or di-substituted phenyl bromide, triflate or iodide in an inert solvent;

b) containing hexamethylphosphoramide and a palladium (O) catalyst, such as tetrakis (triphenylphosphine)palladium; or

c) said solvent containing a palladium (II) catalyst in the presence of lithium chloride and an added inorganic or organic base, such as sodium bicarbonate or triethylamine; and

d) optionally followed by oxidation, hydrolysis or reduction to yield the final desired compound of Formula (IA);

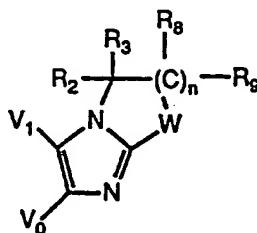
provided that :

when W is $S(O)_m$ and m is 0, n is 1 or 2 and X_2 is 4-pyridyl; the

Formula (F) compounds are treated with a di-substituted phenyl bromide, triflate or iodide wherein the substituents are selected from one of the following combinations: di(C_{1-3} alkylthio), dihalo, (C_{1-3} alkylthio) and C_{1-2} alkoxy, C_{1-3} alkylthio and halo, C_{1-3} alkylthio and C_{1-4} alkyl, or C_{1-2} alkoxy and halo;

further provided that the remaining compounds of Formula (F) when treated with a mono- or di-substituted phenyl bromide, triflate or iodide said mono-substituent is selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, hydrogen, or C_{1-4} alkyl; or di-substituted substituents are selected from C_{1-3} alkylthio, C_{1-3} alkylsulfinyl, C_{1-2} alkoxy, halo, or C_{1-4} alkyl; or

E. When it is required to prepare a compound of Formula (IA) wherein one of R_1 or R_0 is a mono or di-substituted phenyl having at least one 2-alkenyl-1-thio functionality, reacting a compound of Formula (G) as represented by the structure:



Formula (G)

or a pharmaceutically acceptable salt thereof,

wherein:

W is $-CR_5=CR_7-$, $-N=CR_7-$, $-S-$ or $-O-$;

one of V_1 or V_0 is 4-pyridyl or C_{1-4} alkyl-4-pyridyl, provided that when V_1 is C_{1-4} alkyl-4-pyridyl the alkyl substituent is located at the 2-position of the pyridine ring, and the other of V_1 and V_0 is selected from:

(a) monosubstituted phenyl wherein said substituent is mercapto; or

(b) disubstituted phenyl wherein one of said substituents must be mercapto and the other is selected from mercapto, C₁₋₂ alkoxy, halo, or C₁₋₄ alkyl;

provided that:

(1.) when W is -CR₅=CR₇- or -N=CR₇- then

n is 1;

R₃, R₅, R₇ and R₉ are, independently, -H or C₁₋₂ alkyl; and

R₂ and R₈ together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is -S- then

n is 1 or 2;

R₃ and R₉ are, independently, -H or C₁₋₂ alkyl;

further provided that:

(a) when W is -S- and n is 1 then R₂ and R₈ are, independently, -H or C₁₋₂ alkyl or together represent a double bond in the B ring such that the B ring is an aromatic thiazole ring; and

(b) when W is -S- and n is 2 then R₂ and R₈ are, independently, -H or C₁₋₂ alkyl; and

(3.) when W is -O- then

n is 1;

R₃ and R₉ are, independently, -H or C₁₋₂ alkyl; and

R₂ and R₈ represent double bonds in the B ring such that the B ring is an aromatic oxazole ring;

wherein the compound of Formula (G) is placed into solution with a polar solvent and treated with base, such as a metal hydride and the resulting salt form is treated with a 1-halo-2-alkene to yield the desired compound of Formula (IA) having at least one 2-alkenyl-1-thio substituent group on the mono- or di-substituted phenyl; or

F. When it is required to prepare a compound of Formula (IA) wherein one of R₁ or R₉ is a mono- or di-substituted phenyl having at least one 1-alkenyl-1-thio functional group, reacting a compound of Formula (G) as defined above, in a nonprotic solvent, such as tetrahydrofuran, with a strong base, such as lithium diethylamide, at low temperatures to generate the lithium mercaptide salt; alkylating said salt with a trimethylsilylmethylating agent, such as a halide, triflate or acetate derivative, to form

the trimethylsilylmethylthio substituent group; said trimethylsilylmethylthio substituent is deprotonated with addition of said strong base and treated with the appropriate aldehyde or ketone to yield the desired compound of Formula (IA); or

- 5 G. When it is required to prepare a compound of Formula (IA), or (IB) wherein one of R_1 or R_2 is a mono or di-substituted 4-alkylthio compound, which process comprises reacting a corresponding 4-halogen substituted compound of Formula (IA), or (IB) with a metal alkyl-mercaptide salt, such as sodium thioethoxide, in a polar nonprotic solvent, such as dimethylformamide to yield the desired final product
- 10 of Formula (IA), or (IB); or

- H. When it is required to prepare a compound of Formula (IA) wherein the final desired compound has an alkylsulfinyl, 1-alkenyl-1-sulfinyl or 2-alkenyl-1-sulfinyl mono or di-substituted phenyl, or compounds of Formula (IA) wherein W is $S(O)_m$
- 15 and m is 1 which process comprises reacting the corresponding compound of Formula (IA) having a mono- or di-substituted alkylthio, 1-alkenyl-1-thio, or 2-alkenyl-1-thio moiety with an oxidizing agent, such as an organic peracid, or an inorganic agent, such as sodium periodate or hydrogen peroxide; or

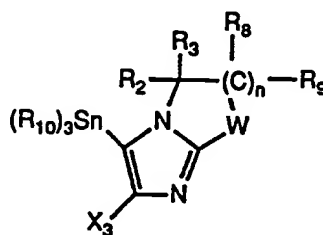
- 20 I. When it is required to prepare a compound of Formula (IA) which process comprises
- a) reacting a compound of Formula (C) as previously defined with a C_{1-5} alkyllithium compound to yield the corresponding lithium reagent by metallation;
 - 25 b) adding excess magnesium halide etherate to the lithium reagent to yield the corresponding Grignard reagent by transmetallation;
 - c) adding the Grignard reagent to an N-acylpyridium salt to yield the corresponding compound of Formula (D) as defined above;
 - d) deacylating and oxidizing the Formula (D) compound followed
 - 30 optionally by hydrolysis, reduction, oxidation, demethylation and acylation of the oxidized compound of Formula (D) to yield the desired final compound of Formula (IA); or

- J. When it is required to prepare a compound of Formula (IA) which process
- 35 comprises
- a) reacting a compound of Formula (C) with a C_{1-5} alkyllithium compound to yield the corresponding lithium reagent by metallation;

b) adding excess magnesium halide or zinc halide etherate to the lithium reagent to yield the corresponding organometallic reagent by transmetallation;

c) adding the organotransmetallated reagent to a 4-bromo, 4-iodopyridine or the triflate ester of a 4-hydroxy pyridine in the presence of palladium (O), such as tetrakis (triphenyl-phosphine)-palladium or a palladium (II) catalyst, in the presence of lithium chloride and a base to yield the corresponding compound of Formula (IA) as defined above; or

K. treating the 3-lithio derivative of a compound of Formula (C), Step J.(a), as previously defined, with a trialkyltin halide, such as n-butyl tin chloride, to yield a compound of Formula (If) having the following formula



Formula (If)

wherein

W is $-\text{CR}_5=\text{CR}_7-$, $-\text{N}=\text{CR}_7-$, $-\text{S}-$ or $-\text{O}-$;

X_3 is

(a) phenyl or monosubstituted phenyl wherein said substituent is selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, or C_{1-4} alkyl; or

(b) disubstituted phenyl wherein said substituents are independently selected from C_{1-3} alkylthio, C_{1-2} alkoxy, halo, C_{1-4} alkyl, or the disubstituents together form a methylene dioxy group;

provided that:

(1.) when W is $-\text{CR}_5=\text{CR}_7-$ or $-\text{N}=\text{CR}_7-$ then

n is 1;

R_3 , R_5 , R_7 and R_9 are, independently, $-\text{H}$ or C_{1-2} alkyl;

R_2 and R_8 together represent a double bond in the B ring such that the B ring is an aromatic pyridine or pyrimidine ring; and

(2.) when W is $-\text{S}-$ or $-\text{O}-$ then

n is 1;

R_3 and R_9 are, independently, $-\text{H}$ or C_{1-2} alkyl; and

R₂ and R₈ are, independently, -H or C₁₋₂ alkyl or together represent a double bond in the B ring such that the B ring is an aromatic thiazole or oxazole ring; and

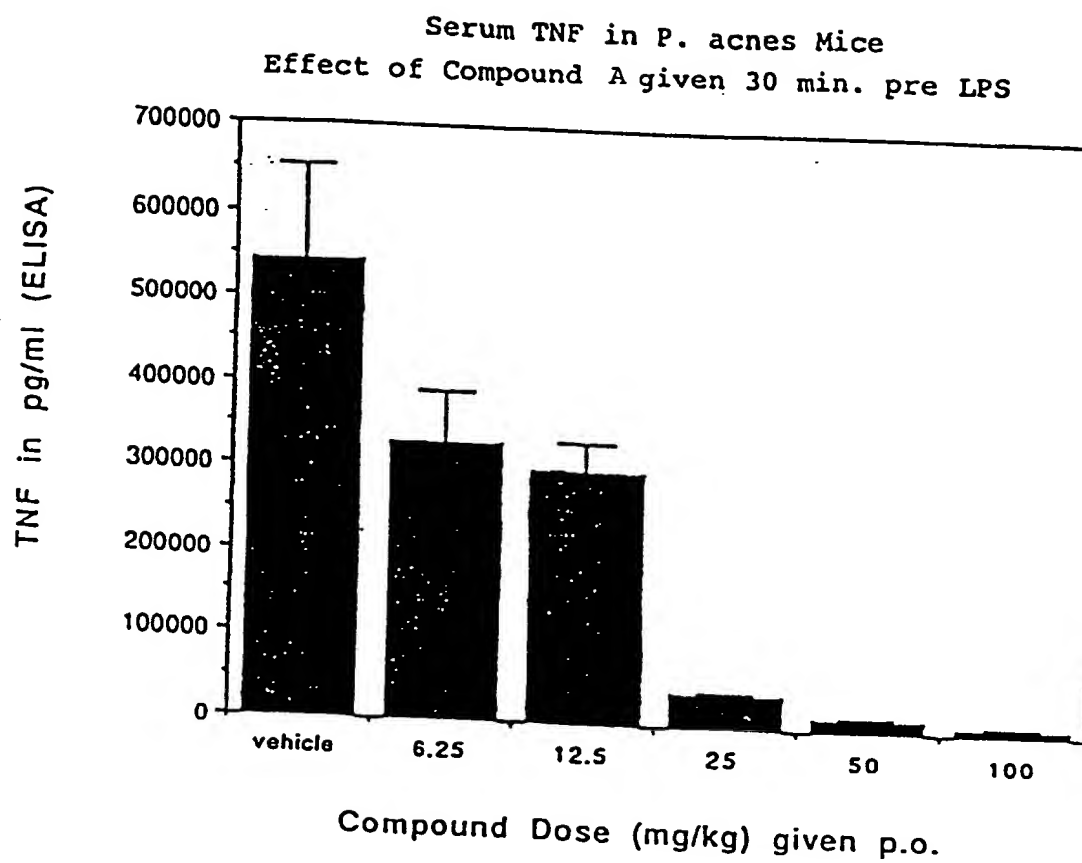
- 5 reacting the Formula (If) compound with a mixture of a
- i) 4-pyridyl halide, preferably iodide, or triflate ester of a hydroxy 4-pyridyl compound; and
 - ii) tetrakis (triphenylphosphine)palladium in a mixture of tetrahydrofuran and hexamethylphosphoramide; or
 - 10 iii) a mixture of i) and a palladium (II) catalyst in the presence of lithium chloride, and a base;
- both optionally followed by hydrolysis, oxidation, or reduction to yield the desired final compound of Formula (IA); or
- 15 L. Treating a compound of Formula (C), as previously defined, with
- i) an excess of bromine to yield a 3-bromo derivative of a Formula (C) compound;
 - ii) treating the 3-bromo derivative by halogen-metal exchange with n-BuLi to yield the corresponding 3-lithio derivative;
 - 20 iii) coupling a compound of step (i) or step (ii) with a substituted 4-halopyridine in the presence of bidentate palladium-(II) or a Ni(II)Cl₂ (1,2-bis-(diphenylphosphino)ethane) catalyst to yield the desired compounds of Formula (IA); or
- 25 M. Treating a compound of Formula (C) wherein X is a 4-pyridyl or mono-C₁₋₄ alkyl-4-pyridyl with
- i) an excess of bromine to yield a 3-bromo derivative of a Formula (C) compound;
 - ii) followed by halogen-metal exchange with n-BuLi to yield the 3-lithio derivative ;
 - 30 iii) coupling a compound of step (i) or (ii) to a substituted halobenzene, preferably iodide, in the presence of bidentate palladium(II) or a Ni(II)Cl₂ (1,2-bis-(diphenylphosphino)ethane) catalyst to yield the desired regioisomer compounds of Formula (IA);
- 35 or
- N. Treating a compound of Formula (C) wherein X is a 4-pyridyl or mono-C₁₋₄ alkyl-4-pyridyl with an excess of bromination to yield a 3-bromo derivative of a

Formula (C) compound and coupling a compound of step (i) or (ii) to a substituted phenyl-trialkyl tin reagent with a palladium (O) catalyst, such as tetrakis (triphenylphosphine)palladium to yield the desired compounds of Formula (IA); or

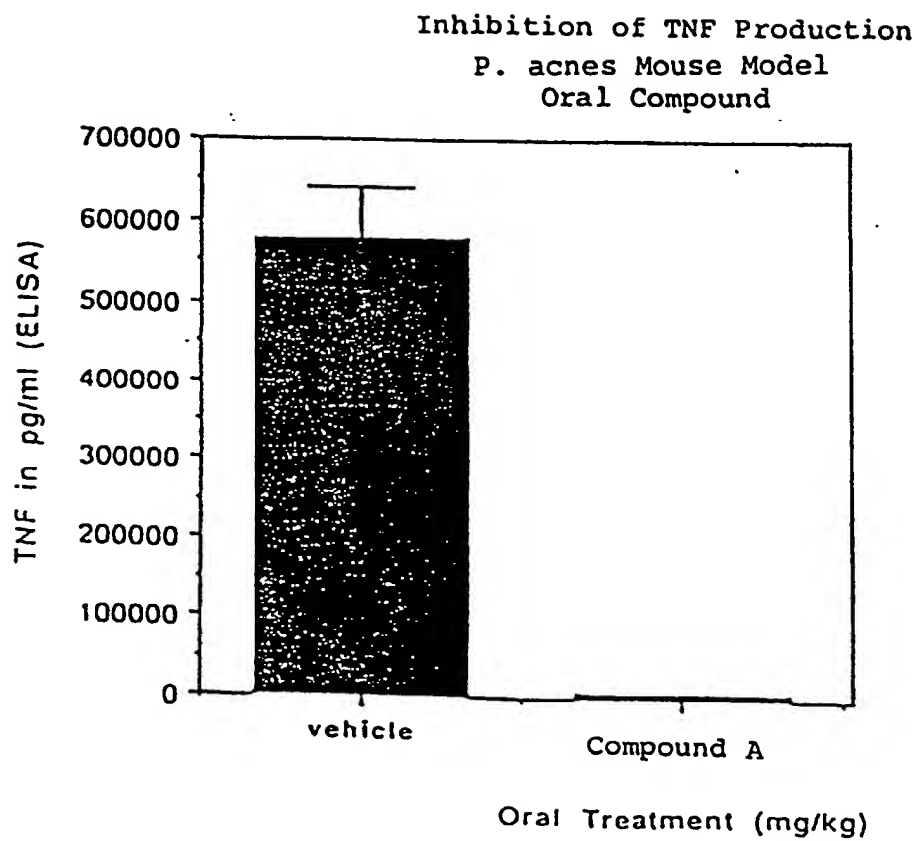
- 5 O. Treating a compound of Formula (C) wherein X is other than a 4-pyridyl or mono-C₁₋₄ alkyl-4-pyridyl with an excess of bromination to yield a 3-bromo derivative of a Formula (C) compound, and coupling to a substituted 4-pyridyl-trialkyl tin reagent with a palladium (O) catalyst, such as tetrakis(triphenylphosphine)palladium, to yield a compound of Formula (IA); or
- 10 P. Coupling a compound of Formula (F) as previously defined, with a halobenzene, such as iodophenyl, in the presence of a palladium (O) catalyst, such as tetrakis (triphenylphosphine)palladium, to yield a compound of Formula (IA); or
- 15 Q. Wherein the desired final product is a compound of Formula (IA) wherein R or R¹ is phenyl substituted with a substituted disulfide group are prepared by treating a compound of Formula (G) by mild air oxidation; or to yield the nonsymmetrical disulfide compounds of Formula (IA) wherein the disulfide is Z and Z is -S-S-Z₁; Z₁ is C₁₋₉ alkyl or phenyl; are prepared by reacting the appropriate sulfhydryl compound
- 20 of Formula (G) with the appropriate sulfenyl halide in an ethereal solvent to afford compounds of Formula (I) wherein one of R or R¹ is phenyl substituted with one or more alkyl-dithio or aryl-dithio groups.

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Figure 1

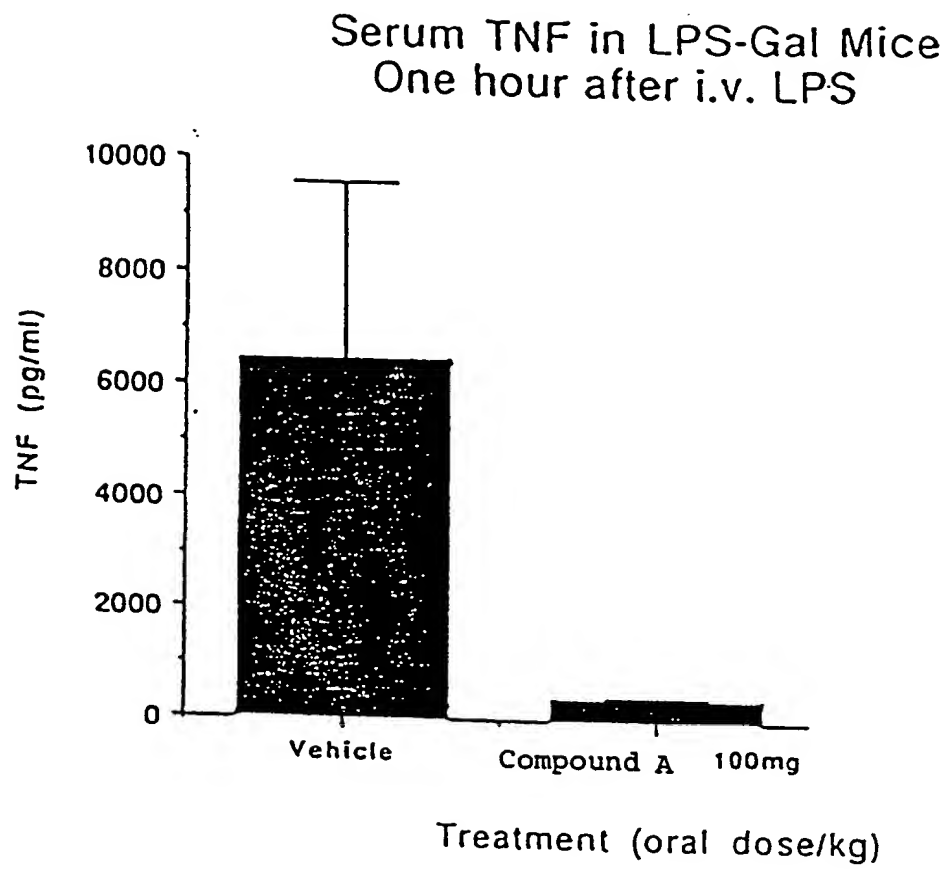


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Figure 2



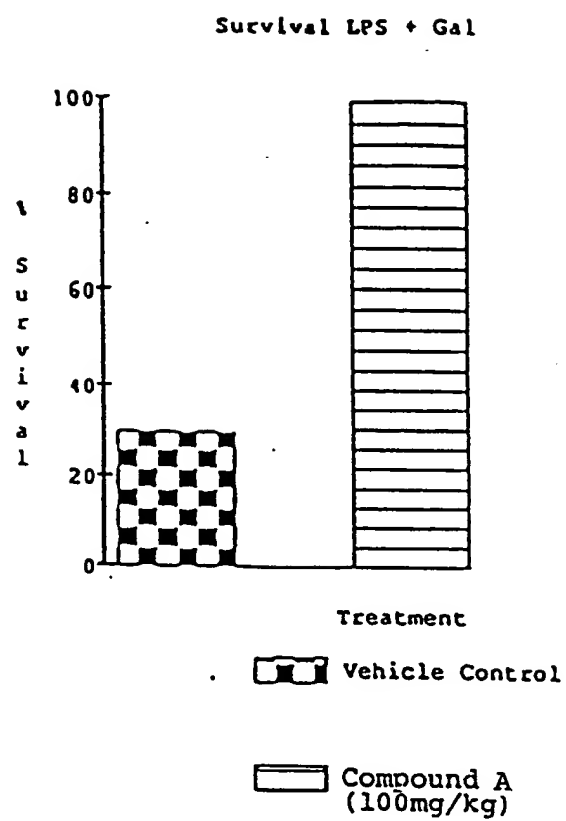
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Figure 3



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Figure 4



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US90/03367

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ¹ According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5) A61K-31/38; 31/415; 31/435, 31/505 C07D-471/04; 487/04; 498/04		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System ¹	Classification Symbols	
U.S.	546/121, 271; 544/281 514/258, 300, 338	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category ⁸	Citation of Document, ¹³ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹⁴
A	US, A, 4,810,711 (GEORGE ET AL) 07 March 1989 All.	1-29
A	US, A, 4,791,202 (YAMANAKA ET AL) 13 December 1988 All.	1-29
&	US, A, 4,719,218 (BENDER ET AL) 12 January 1988 All.	1-29
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IV. CERTIFICATION		
Date of the Actual Completion of the International Search ³	Date of Mailing of this International Search Report ²	
27 NOVEMBER 1990	06 DEC 1990	
International Searching Authority ¹	Signature of Authorized Officer ¹⁰	
ISA/US	Andrew Robinson Johann Richter	

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